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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: David WENSBO

Title: *FUSED HETEROCYCLIC COMPOUNDS AND THEIR USE AS  
METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS*

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**PROVISIONAL PATENT APPLICATION**  
**TRANSMITTAL**

Mail Stop PROVISIONAL PATENT APPLICATION  
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Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(c) is the provisional patent application  
of:

David WENSBO

☐ Applicant claims small entity status under 37 CFR 1.27(c)(1).

Enclosed are:

☒ Specification, Claim(s), and Abstract (58 pages).

☐ Assignment of the invention to AstraZeneca and NPS Pharmaceuticals, Inc..

☒ Application Data Sheet (37 CFR 1.76).

The filing fee is calculated below:

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<input type="checkbox"/> Small Entity Fees Apply (subtract ½ of above):		=	\$0.00
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- [ ] A check in the amount of \$0.00 to cover the filing fee is enclosed.
- [ X ] The required filing fees are not enclosed but will be submitted in response to the Notice to File Missing Parts of Application.
- [ X ] Further, Applicant, by and through his attorney of record, hereby expressly abandons the application as of the filing date of this letter. This is an abandonment of the application only, and is not to be construed as an abandonment of the invention disclosed in the application. It is respectfully requested that the Office acknowledge abandonment of the application as of the filing date of this letter in a communication mailed to the undersigned.
- [ ] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date 19 February 2004

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**U.S. PROVISIONAL PATENT APPLICATION**

**for**

**FUSED HETEROCYCLIC COMPOUNDS AND THEIR USE AS  
METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS**

Inventors: David WENSBO

## **FUSED HETEROCYCLIC COMPOUNDS AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS**

### **BACKGROUND OF THE INVENTION**

**[0001]** The present invention relates to a new heterocyclic compounds, to pharmaceutical compositions containing the compounds and to the use of the compounds in therapies related to metabotropic glutamate receptor-mediated conditions. The present invention further relates to processes for the preparation of the compounds and to new intermediates used in the preparation thereof.

**[0002]** Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects on central neurons by binding to and thereby activating cell surface receptors. These receptors have been divided into two major classes, the ionotropic and metabotropic glutamate receptors, based on the structural features of the receptor proteins, the means by which the receptors transduce signals into the cell, and pharmacological profiles.

**[0003]** The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that activate a variety of intracellular second messenger systems following the binding of glutamate. Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C; increases in phosphoinositide (PI) hydrolysis; intracellular calcium release; activation of phospholipase D; activation or inhibition of adenylyl cyclase; increases or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase; increases in the formation of cyclic guanosine monophosphate (cGMP); activation of phospholipase A<sub>2</sub>; increases in arachidonic acid release; and increases or decreases in the activity of voltage- and ligand-gated ion channels. Schoepp *et al.*, *Trends Pharmacol. Sci.* 14:13 (1993), Schoepp, *Neurochem. Int.* 24:439 (1994), Pin *et al.*, *Neuropharmacology* 34:1 (1995), Bordi and Ugolini, *Prog. Neurobiol.* 59:55 (1999).

**[0004]** Eight distinct mGluR subtypes, termed mGluR1 through mGluR8, have been identified by molecular cloning. Nakanishi, *Neuron* 13:1031 (1994), Pin *et al.*, *Neuropharmacology* 34:1 (1995), Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995). Further receptor diversity occurs via expression of alternatively spliced forms of certain mGluR subtypes. Pin *et al.*, *PNAS* 89:10331 (1992), Minakami *et al.*, *BBRC* 199:1136 (1994), Joly *et al.*, *J. Neurosci.* 15:3970 (1995).

**[0005]** Metabotropic glutamate receptor subtypes may be subdivided into three groups, Group I, Group II, and Group III mGluRs, based on amino acid sequence homology, the second messenger systems utilized by the receptors, and by their pharmacological characteristics. Group I mGluR comprises mGluR1, mGluR5 and their alternatively spliced variants. The binding of agonists to these receptors results in the activation of phospholipase C and the subsequent mobilization of intracellular calcium.

#### **Neurological, psychiatric and pain disorders.**

**[0006]** Attempts at elucidating the physiological roles of Group I mGluRs suggest that activation of these receptors elicits neuronal excitation. Various studies have demonstrated that Group I mGluRs agonists can produce postsynaptic excitation upon application to neurons in the hippocampus, cerebral cortex, cerebellum, and thalamus, as well as other CNS regions. Evidence indicates that this excitation is due to direct activation of postsynaptic mGluRs, but it also has been suggested that activation of presynaptic mGluRs occurs, resulting in increased neurotransmitter release. Baskys, *Trends Pharmacol. Sci.* 15:92 (1992), Schoepp, *Neurochem. Int.* 24:439 (1994), Pin *et al.*, *Neuropharmacology* 34:1(1995), Watkins *et al.*, *Trends Pharmacol. Sci.* 15:33 (1994).

**[0007]** Metabotropic glutamate receptors have been implicated in a number of normal processes in the mammalian CNS. Activation of mGluRs has been shown to be required for induction of hippocampal long-term potentiation and cerebellar long-term depression. Bashir *et al.*, *Nature* 363:347 (1993), Bortolotto *et al.*, *Nature* 368:740 (1994), Aiba *et al.*, *Cell* 79:365 (1994), Aiba *et al.*, *Cell* 79:377 (1994). A role for mGluR activation in nociception and analgesia also has been demonstrated.

Meller *et al.*, *Neuroreport* 4: 879 (1993), Bordi and Ugolini, *Brain Res.* 871:223 (1999). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control and control of the vestibulo-ocular reflex. Nakanishi, *Neuron* 13: 1031 (1994), Pin *et al.*, *Neuropharmacology* 34:1, Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995).

[0008] Further, Group I metabotropic glutamate receptors have been suggested to play roles in a variety of acute and chronic pathophysiological processes and disorders affecting the CNS. These include stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy, neurodegenerative disorders such as Alzheimer's disease, psychiatric disorders and pain. Schoepp *et al.*, *Trends Pharmacol. Sci.* 14:13 (1993), Cunningham *et al.*, *Life Sci.* 54:135 (1994), Hollman *et al.*, *Ann. Rev. Neurosci.* 17:31 (1994), Pin *et al.*, *Neuropharmacology* 34:1 (1995), Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995), Spooren *et al.*, *Trends Pharmacol. Sci.* 22:331 (2001), Gasparini *et al.* *Curr. Opin. Pharmacol.* 2:43 (2002), Neugebauer *Pain* 98:1 (2002). Much of the pathology in these conditions is thought to be due to excessive glutamate-induced excitation of CNS neurons. Because Group I mGluRs appear to increase glutamate-mediated neuronal excitation via postsynaptic mechanisms and enhanced presynaptic glutamate release, their activation probably contributes to the pathology. Accordingly, selective antagonists of Group I mGluR receptors could be therapeutically beneficial in all conditions underlain by excessive glutamate-induced excitation of CNS neurons, specifically as neuroprotective agents, analgesics or anticonvulsants.

[0009] Recent advances in the elucidation of the neurophysiological roles of metabotropic glutamate receptors generally and Group I in particular, have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders.

#### **Gastro intestinal disorders**

[0010] The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the



mechanical barrier is temporarily lost at such times, an event hereinafter referred to as “reflux”.

[0011] Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535*, has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

[0012] The novel compounds according to the present invention are useful for the inhibition of transient lower esophageal sphincter relaxations (TLESRs) and thus for treatment of gastro-esophageal reflux disorder (GERD).

[0013] The term “TLESR”, transient lower esophageal sphincter relaxations, is herein defined in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

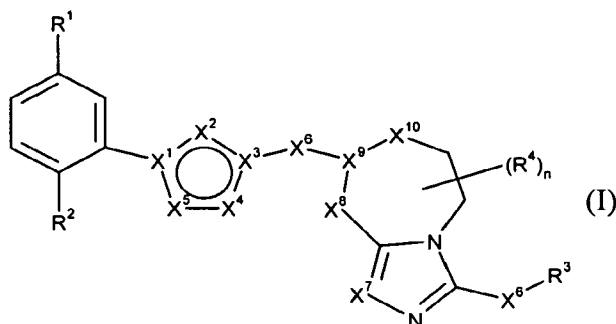
[0014] The term “reflux” is herein defined as fluid from the stomach being able to pass into the esophagus, since the mechanical barrier is temporarily lost at such times.

[0015] The term “GERD”, gastro-esophageal reflux disease, is herein defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

[0016] The physiological and pathophysiological significance of mGluR agonists and antagonists that display a high selectivity for mGluR subtypes, particularly the Group I receptor subtype, warrant a continued need for new agonists and antagonists.

## SUMMARY OF THE INVENTION

[0017] The present invention relates to compounds of formula I:



[0018]

[0019] In Formula I,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , and  $X^5$  are independently selected from the group consisting of C,  $CR^5$ , N, O, and S, wherein at least one of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , and  $X^5$  is not N;  $X^6$  is selected from the group consisting of a bond and  $CR^5R^6$ ;  $X^7$  is  $CR^5$  or N;  $X^8$  is selected from the group consisting of a bond,  $CR^5R^6$ ,  $NR^5$ , O, S, SO, and  $SO_2$ ;

[0020]  $X^9$  is  $CR^5$  or N; and  $X^{10}$  is selected from the group consisting of a bond,  $CR^5R^6$ ,  $(CR^5R^6)_2$ , O, S, and  $NR^5$ .

[0021]  $R^1$  is selected from the group consisting of hydroxy, halo, nitro,  $C_{1-6}$ alkylhalo,  $OC_{1-6}$ alkylhalo,  $C_{1-6}$ alkyl,  $OC_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $OC_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $OC_{2-6}$ alkynyl,  $C_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $OC_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $C_{0-6}$ alkylaryl,  $OC_{0-6}$ alkylaryl, CHO,  $(CO)R^5$ ,  $O(CO)R^5$ ,  $O(CO)OR^5$ ,  $O(CN)OR^5$ ,  $C_{1-6}$ alkyl $OR^5$ ,  $OC_{2-6}$ alkyl $OR^5$ ,  $C_{1-6}$ alkyl $(CO)R^5$ ,  $OC_{1-6}$ alkyl $(CO)R^5$ ,  $C_{0-6}$ alkyl $CO_2R^5$ ,  $OC_{1-6}$ alkyl $CO_2R^5$ ,  $C_{0-6}$ alkylcyano,  $OC_{2-6}$ alkylcyano,  $C_{0-6}$ alkyl $NR^5R^6$ ,  $OC_{2-6}$ alkyl $NR^5R^6$ ,  $C_{1-6}$ alkyl $(CO)NR^5R^6$ ,  $OC_{1-6}$ alkyl $(CO)NR^5R^6$ ,  $C_{0-6}$ alkyl $NR^5(CO)R^6$ ,  $OC_{2-6}$ alkyl $NR^5(CO)R^6$ ,  $C_{0-6}$ alkyl $NR^5(CO)NR^5R^6$ ,  $C_{0-6}$ alkyl $SR^5$ ,  $OC_{2-6}$ alkyl $SR^5$ ,  $C_{0-6}$ alkyl $(SO)R^5$ ,  $OC_{2-6}$ alkyl $(SO)R^5$ ,  $C_{0-6}$ alkyl $SO_2R^5$ ,  $OC_{2-6}$ alkyl $SO_2R^5$ ,  $C_{0-6}$ alkyl $(SO_2)NR^5R^6$ ,  $OC_{2-6}$ alkyl $(SO_2)NR^5R^6$ ,  $C_{0-6}$ alkyl $NR^5(SO_2)R^6$ ,  $OC_{2-6}$ alkyl $NR^5(SO_2)R^6$ ,  $C_{0-6}$ alkyl $NR^5(SO_2)NR^5R^6$ ,  $OC_{2-6}$ alkyl $NR^5(SO_2)NR^5R^6$ ,  $(CO)NR^5R^6$ ,  $O(CO)NR^5R^6$ ,  $NR^5OR^6$ ,  $C_{0-6}$ alkyl $NR^5(CO)OR^6$ ,  $OC_{2-6}$ alkyl $NR^5(CO)OR^6$ ,  $SO_3R^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A, as defined below.

**[0022]**  $R^2$  is selected from the group consisting of hydrogen, hydroxy, halo, nitro,  $C_{1-6}$ alkylhalo,  $OC_{1-6}$ alkylhalo,  $C_{1-6}$ alkyl,  $OC_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $OC_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $OC_{2-6}$ alkynyl,  $C_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $OC_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $C_{0-6}$ alkylaryl,  $OC_{0-6}$ alkylaryl, CHO,  $(CO)R^5$ ,  $O(CO)R^5$ ,  $O(CO)OR^5$ ,  $O(CN)OR^5$ ,  $C_{1-6}$ alkylOR<sup>5</sup>,  $OC_{2-6}$ alkylOR<sup>5</sup>,  $C_{1-6}$ alkyl(CO)R<sup>5</sup>,  $OC_{1-6}$ alkyl(CO)R<sup>5</sup>,  $C_{0-6}$ alkylCO<sub>2</sub>R<sup>5</sup>,  $OC_{1-6}$ alkylCO<sub>2</sub>R<sup>5</sup>,  $C_{0-6}$ alkylcyano,  $OC_{2-6}$ alkylcyano,  $C_{0-6}$ alkylNR<sup>5</sup>R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>R<sup>6</sup>,  $C_{1-6}$ alkyl(CO)NR<sup>5</sup>R<sup>6</sup>,  $OC_{1-6}$ alkyl(CO)NR<sup>5</sup>R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(CO)R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)NR<sup>5</sup>R<sup>6</sup>,  $C_{0-6}$ alkylSR<sup>5</sup>,  $OC_{2-6}$ alkylSR<sup>5</sup>,  $C_{0-6}$ alkyl(SO)R<sup>5</sup>,  $OC_{2-6}$ alkyl(SO)R<sup>5</sup>,  $C_{0-6}$ alkylSO<sub>2</sub>R<sup>5</sup>,  $OC_{2-6}$ alkylSO<sub>2</sub>R<sup>5</sup>,  $C_{0-6}$ alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $OC_{2-6}$ alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $(CO)NR^5R^6$ ,  $O(CO)NR^5R^6$ ,  $NR^5OR^6$ ,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)OR<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(CO)OR<sup>6</sup>,  $SO_3R^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A.

**[0023]**  $R^3$  is a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A.

**[0024]**  $R^4$  is selected from the group consisting of hydroxy, halo, nitro,  $C_{1-6}$ alkylhalo,  $OC_{1-6}$ alkylhalo,  $C_{1-6}$ alkyl,  $OC_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $OC_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $OC_{2-6}$ alkynyl,  $C_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $OC_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $C_{0-6}$ alkylaryl,  $OC_{0-6}$ alkylaryl, CHO,  $(CO)R^5$ ,  $O(CO)R^5$ ,  $O(CO)OR^5$ ,  $O(CN)OR^5$ ,  $C_{1-6}$ alkylOR<sup>5</sup>,  $OC_{2-6}$ alkylOR<sup>5</sup>,  $C_{1-6}$ alkyl(CO)R<sup>5</sup>,  $OC_{1-6}$ alkyl(CO)R<sup>5</sup>,  $C_{0-6}$ alkylCO<sub>2</sub>R<sup>5</sup>,  $OC_{1-6}$ alkylCO<sub>2</sub>R<sup>5</sup>,  $C_{0-6}$ alkylcyano,  $OC_{2-6}$ alkylcyano,  $C_{0-6}$ alkylNR<sup>5</sup>R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>R<sup>6</sup>,  $C_{1-6}$ alkyl(CO)NR<sup>5</sup>R<sup>6</sup>,  $OC_{1-6}$ alkyl(CO)NR<sup>5</sup>R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(CO)R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)NR<sup>5</sup>R<sup>6</sup>,  $C_{0-6}$ alkylSR<sup>5</sup>,  $OC_{2-6}$ alkylSR<sup>5</sup>,  $C_{0-6}$ alkyl(SO)R<sup>5</sup>,  $OC_{2-6}$ alkyl(SO)R<sup>5</sup>,  $C_{0-6}$ alkylSO<sub>2</sub>R<sup>5</sup>,  $OC_{2-6}$ alkylSO<sub>2</sub>R<sup>5</sup>,  $C_{0-6}$ alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $OC_{2-6}$ alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>,  $(CO)NR^5R^6$ ,  $O(CO)NR^5R^6$ ,  $NR^5OR^6$ ,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)OR<sup>6</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(CO)OR<sup>6</sup>,  $SO_3R^5$  and a 5- or 6-membered ring containing atoms

independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A.

**[0025]**  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl and aryl.

**[0026]** A is selected from the group consisting of hydrogen, hydroxy, halo, nitro,  $C_{1-6}$ alkylhalo,  $OC_{1-6}$ alkylhalo,  $C_{1-6}$ alkyl,  $OC_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $OC_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $OC_{2-6}$ alkynyl,  $C_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $OC_{0-6}$ alkyl $C_{3-6}$ cycloalkyl,  $C_{0-6}$ alkylaryl,  $OC_{0-6}$ alkylaryl, CHO,  $(CO)R^5$ ,  $O(CO)R^5$ ,  $O(CO)OR^5$ ,  $O(CN)OR^5$ ,  $C_{1-6}$ alkylOR<sup>5</sup>,  $OC_{2-6}$ alkylOR<sup>5</sup>,  $C_{1-6}$ alkyl(CO)R<sup>5</sup>,  $OC_{1-6}$ alkyl(CO)R<sup>5</sup>,  $C_{0-6}$ alkylCO<sub>2</sub>R<sup>5</sup>,  $OC_{1-6}$ alkylCO<sub>2</sub>R<sup>5</sup>,  $C_{0-6}$ alkylcyano,  $OC_{2-6}$ alkylcyano,  $C_{0-6}$ alkylNR<sup>5</sup>R<sup>5</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>R<sup>8</sup>,  $C_{1-6}$ alkyl(CO)NR<sup>5</sup>R<sup>8</sup>,  $OC_{1-6}$ alkyl(CO)NR<sup>5</sup>R<sup>8</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)R<sup>8</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(CO)R<sup>8</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)NR<sup>5</sup>R<sup>8</sup>,  $C_{0-6}$ alkylSR<sup>5</sup>,  $OC_{2-6}$ alkylSR<sup>5</sup>,  $C_{0-6}$ alkyl(SO)R<sup>5</sup>,  $OC_{2-6}$ alkyl(SO)R<sup>5</sup>,  $C_{0-6}$ alkylSO<sub>2</sub>R<sup>5</sup>,  $OC_{2-6}$ alkylSO<sub>2</sub>R<sup>5</sup>,  $C_{0-6}$ alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>8</sup>,  $OC_{2-6}$ alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>8</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>8</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>8</sup>,  $C_{0-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>8</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>8</sup>,  $(CO)NR^5R^8$ ,  $O(CO)NR^5R^8$ ,  $NR^5OR^8$ ,  $C_{0-6}$ alkylNR<sup>5</sup>(CO)OR<sup>8</sup>,  $OC_{2-6}$ alkylNR<sup>5</sup>(CO)OR<sup>8</sup>, SO<sub>3</sub>R<sup>5</sup> and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S.

**[0027]** Variable n is 0, 1, 2, 3, or 4.

**[0028]** In a further aspect of the invention there is provided pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable diluent, excipient and/or inert carrier.

**[0029]** In yet a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula I for use in the treatment of mGluR5 receptor mediated disorders, and for use in the treatment of neurological disorders, psychiatric disorders, gastrointestinal disorders and pain disorders.

**[0030]** In still a further aspect of the invention there is provided the compound of formula I for use in therapy, especially for the treatment of mGluR5 receptor mediated disorders, and for the treatment of neurological disorders, psychiatric disorders, gastrointestinal disorders and pain disorders.

**[0031]** In another aspect of the invention there is provided processes for the preparation of compounds of formula I and the intermediates used in the preparation thereof.

**[0032]** These and other aspects of the present invention are described in greater detail herein below.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

**[0033]** The object of the present invention is to provide compounds exhibiting an activity at metabotropic glutamate receptors (mGluRs), especially at the mGluR5 receptors.

**[0034]** Listed below are definitions of various terms used in the specification and claims to describe the present invention.

**[0035]** For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

**[0036]** For the avoidance of doubt it is to be understood that in this specification 'C<sub>1-6</sub>' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms. Similarly 'C<sub>1-3</sub>' means a carbon group having 1, 2, or 3 carbon atoms

**[0037]** In the case where a subscript is the integer 0 (zero) the group to which the subscript refers indicates that the group is absent.

**[0038]** In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C<sub>1-3</sub>alkyl has 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl or i-propyl.

**[0039]** In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C<sub>3-7</sub>cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0040] In this specification, unless stated otherwise, the term “alkoxy” includes both straight or branched alkoxy groups. C<sub>1-3</sub>alkoxy may be, but is not limited to methoxy, ethoxy, n-propoxy or i-propoxy.

[0041] In this specification, unless stated otherwise, the term “bond” may be a saturated or unsaturated bond.

[0042] In this specification, unless stated otherwise, the term “halo” and “halogen” may be fluoro, chloro, bromo or iodo.

[0043] In this specification, unless stated otherwise, the term “alkylhalo” means an alkyl group as defined above, which is substituted with halo as described above. The term “C<sub>1-6</sub>alkylhalo” may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term “OC<sub>1-6</sub>alkylhalo” may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

[0044] In this specification, unless stated otherwise, the term “alkenyl” includes both straight and branched chain alkenyl groups. The term “C<sub>2-6</sub>alkenyl” refers to an alkenyl group having 2 to 6 carbon atoms and one or two double bonds, and may be, but is not limited to vinyl, allyl, propenyl, i-propenyl, butenyl, i-butenyl, crotyl, pentenyl, i-pentenyl and hexenyl.

[0045] In this specification, unless stated otherwise, the term “alkynyl” includes both straight and branched chain alkynyl groups. The term C<sub>2-6</sub>alkynyl having 2 to 6 carbon atoms and one or two triple bonds, and may be, but is not limited to ethynyl, propargyl, butynyl, i-butynyl, pentynyl, i-pentynyl and hexynyl.

[0046] In this specification unless otherwise stated the term “aryl” refers to an optionally substituted monocyclic or bicyclic hydrocarbon ring system containing at least one unsaturated aromatic ring. Examples and suitable values of the term “aryl” are phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indyl and indenyl.

[0047] In this specification, unless stated otherwise, the term “heteroaryl” refers to an optionally substituted monocyclic or bicyclic unsaturated, ring system containing at least one heteroatom selected independently from N, O or S. Examples of “heteroaryl” may be, but are not limited to thiophene, thienyl, pyridyl, thiazolyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrazolyl,

imidazolonyl, oxazolonyl, thiazolonyl, tetrazolyl and thiadiazolyl, benzoimidazolyl, benzooxazolyl, tetrahydrotriazolopyridyl, tetrahydrotriazolopyrimidinyl, benzofuryl, indolyl, isoindolyl, pyridonyl, pyridazinyl, pyrimidinyl, imidazopyridyl, oxazolopyridyl, thiazolopyridyl, pyridyl, imidazopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl and purinyl.

**[0048]** In this specification, unless stated otherwise, the term “alkylaryl”, “alkylheteroaryl ” and “alkylcycloalkyl ” refer to a substituent that is attached via the alkyl group to an aryl, heteroaryl and cycloalkyl group.

**[0049]** In this specification, unless stated otherwise, the term “heterocycloalkyl” refers to an optionally substituted, saturated cyclic hydrocarbon ring system wherein one or more of the carbon atoms are replaced with heteroatom. The term “heterocycloalkyl” includes but is not limited to pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran, tetrahydrothiopyran.

**[0050]** In this specification, unless stated otherwise the term “5- or 6-membered ring containing atoms independently selected from C, N, O or S”, includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings, which may be saturated, partially saturated or unsaturated. Examples of such rings may be, but are not limited to furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, imidazolidinyl, imidazoliny, triazolyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyran, thiomorpholinyl, phenyl, cyclohexyl, cyclopentyl and cyclohexenyl.

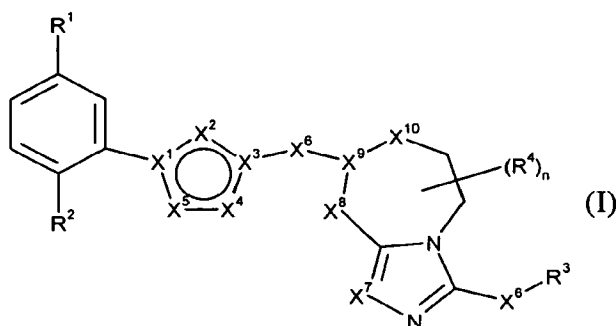
**[0051]** In this specification, unless stated otherwise, the term “=NR<sup>5</sup>” and “=NOR<sup>5</sup>” include imino- and oximogroups carrying an R<sup>5</sup> substituent and may be, or be part of, groups including, but not limited to iminoalkyl, iminohydroxy, iminoalkoxy, amidine, hydroxyamidine and alkoxyamidine.

**[0052]** In the case where a subscript is the integer 0 (zero) the group to which the subscript refers, indicates that the group is absent, i.e. there is a direct bond between the groups.

**[0053]** In this specification unless stated otherwise the term “fused rings” refers to two rings which share 2 common atoms.

**[0054]** In this specification, unless stated otherwise, the term “bridge” means a molecular fragment, containing one or more atoms, or a bond, which connects two remote atoms in a ring, thus forming either bi- or tricyclic systems.

**[0055]** One embodiment of the invention relates to compounds of Formula I and their pharmaceutically acceptable salts and hydrates:



**[0056]** In Formula I,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , and  $X^5$  are independently selected from the group consisting of C,  $CR^5$ , N, O, and S, wherein at least one of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , and  $X^5$  is not N;  $X^6$  is selected from the group consisting of a bond and  $CR^5R^6$ ;  $X^7$  is  $CR^5$  or N, preferably N;  $X^8$  is selected from the group consisting of a bond,  $CR^5R^6$ ,  $NR^5$ , O, S, SO, and  $SO_2$ . Preferably,  $X^8$  is a bond,  $CR^5R^6$ ,  $NR^5$ , O, or S.  $X^9$  is  $CR^5$  or N and  $X^{10}$  is selected from the group consisting of a bond,  $CR^5R^6$ ,  $(CR^5R^6)_2$ , O, S, and  $NR^5$ , preferably a bond,  $CR^5R^6$ ,  $(CR^5R^6)_2$ , O, or S.

**[0057]** R<sup>1</sup> is selected from the group consisting of hydroxy, halo, nitro, C<sub>1</sub>-alkylhalo, OC<sub>1-6</sub>alkylhalo, C<sub>1-6</sub>alkyl, OC<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, OC<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, OC<sub>2-6</sub>alkynyl, C<sub>0-6</sub>alkylC<sub>3-6</sub>cycloalkyl, OC<sub>0-6</sub>alkylC<sub>3-6</sub>cycloalkyl, C<sub>0-6</sub>alkylaryl, OC<sub>0-6</sub>alkylaryl, CHO, (CO)R<sup>5</sup>, O(CO)R<sup>5</sup>, O(CO)OR<sup>5</sup>, O(CN)OR<sup>5</sup>, C<sub>1-6</sub>alkylOR<sup>5</sup>, OC<sub>2-6</sub>alkylOR<sup>5</sup>, C<sub>1-6</sub>alkyl(CO)R<sup>5</sup>, OC<sub>1-6</sub>alkyl(CO)R<sup>5</sup>, C<sub>0-6</sub>alkylCO<sub>2</sub>R<sup>5</sup>, OC<sub>1-6</sub>alkylCO<sub>2</sub>R<sup>5</sup>, C<sub>0-6</sub>alkylcyano, OC<sub>2-6</sub>alkylcyano, C<sub>0-6</sub>alkylNR<sup>5</sup>R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>R<sup>6</sup>, C<sub>1-6</sub>alkyl(CO)NR<sup>5</sup>R<sup>6</sup>, OC<sub>1-6</sub>alkyl(CO)NR<sup>5</sup>R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(CO)R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>(CO)R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(CO)NR<sup>5</sup>R<sup>6</sup>, C<sub>0-6</sub>alkylSR<sup>5</sup>, OC<sub>2-6</sub>alkylSR<sup>5</sup>, C<sub>0-6</sub>alkyl(SO)R<sup>5</sup>, OC<sub>2-6</sub>alkyl(SO)R<sup>5</sup>, C<sub>0-6</sub>alkylSO<sub>2</sub>R<sup>5</sup>, OC<sub>2-6</sub>alkylSO<sub>2</sub>R<sup>5</sup>, C<sub>0-6</sub>alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, OC<sub>2-6</sub>alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, (CO)NR<sup>5</sup>R<sup>6</sup>, O(CO)NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>OR<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(CO)OR<sup>6</sup>, OC<sub>2-</sub>



$_{6\text{alkyl}}\text{NR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A, as defined below. Preferably,  $\text{R}^1$  is halo,  $\text{C}_{1-6}\text{alkylhalo}$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ , or  $\text{C}_{0-6}\text{alkylcyano}$ .

**[0058]**  $\text{R}^2$  is selected from the group consisting of hydrogen, hydroxy, halo, nitro,  $\text{C}_{1-6}\text{alkylhalo}$ ,  $\text{OC}_{1-6}\text{alkylhalo}$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{OC}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{OC}_{2-6}\text{alkynyl}$ ,  $\text{C}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{OC}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{C}_{0-6}\text{alkylaryl}$ ,  $\text{OC}_{0-6}\text{alkylaryl}$ ,  $\text{CHO}$ ,  $(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{OR}^5$ ,  $\text{O}(\text{CN})\text{OR}^5$ ,  $\text{C}_{1-6}\text{alkylOR}^5$ ,  $\text{OC}_{2-6}\text{alkylOR}^5$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylcyano}$ ,  $\text{OC}_{2-6}\text{alkylcyano}$ ,  $\text{C}_{0-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylSR}^5$ ,  $\text{OC}_{2-6}\text{alkylSR}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{NR}^5\text{OR}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A. Preferably,  $\text{R}^2$  is hydrogen or halo.

**[0059]**  $\text{R}^3$  is a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A. Preferably,  $\text{R}^3$  is a 6-membered ring.

**[0060]**  $\text{R}^4$  is selected from the group consisting of hydroxy, halo, nitro,  $\text{C}_{1-6}\text{alkylhalo}$ ,  $\text{OC}_{1-6}\text{alkylhalo}$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{OC}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{OC}_{2-6}\text{alkynyl}$ ,  $\text{C}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{OC}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{C}_{0-6}\text{alkylaryl}$ ,  $\text{OC}_{0-6}\text{alkylaryl}$ ,  $\text{CHO}$ ,  $(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{OR}^5$ ,  $\text{O}(\text{CN})\text{OR}^5$ ,  $\text{C}_{1-6}\text{alkylOR}^5$ ,  $\text{OC}_{2-6}\text{alkylOR}^5$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylcyano}$ ,  $\text{OC}_{2-6}\text{alkylcyano}$ ,  $\text{C}_{0-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylSR}^5$ ,  $\text{OC}_{2-6}\text{alkylSR}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{NR}^5\text{OR}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A.

$\text{C}_6\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{NR}^5\text{OR}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A.  $\text{R}^4$ , when not hydrogen, preferably is  $\text{C}_{1-6}\text{alkylhalo}$  or  $\text{C}_{1-6}\text{alkyl}$ .

**[0061]**  $\text{R}^5$  and  $\text{R}^6$  are independently selected from the group consisting of hydrogen,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{3-7}\text{cycloalkyl}$  and aryl. Preferably,  $\text{R}^5$  and  $\text{R}^6$  are selected from hydrogen and  $\text{C}_{1-6}\text{alkyl}$ .

**[0062]** A is selected from the group consisting of hydrogen, hydroxy, halo, nitro,  $\text{C}_{1-6}\text{alkylhalo}$ ,  $\text{OC}_{1-6}\text{alkylhalo}$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{OC}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{OC}_{2-6}\text{alkynyl}$ ,  $\text{C}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{OC}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{C}_{0-6}\text{alkylaryl}$ ,  $\text{OC}_{0-6}\text{alkylaryl}$ ,  $\text{CHO}$ ,  $(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{OR}^5$ ,  $\text{O}(\text{CN})\text{OR}^5$ ,  $\text{C}_{1-6}\text{alkylOR}^5$ ,  $\text{OC}_{2-6}\text{alkylOR}^5$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylcyano}$ ,  $\text{OC}_{2-6}\text{alkylcyano}$ ,  $\text{C}_{0-6}\text{alkylNR}^5\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylNR}^5\text{R}^8$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{R}^8$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{R}^8$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{C}_{0-6}\text{alkylSR}^5$ ,  $\text{OC}_{2-6}\text{alkylSR}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^8$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^8$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{NR}^5\text{OR}^8$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{OR}^8$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{OR}^8$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S. Preferred values for A are hydrogen and halo.

**[0063]** Variable n is 0, 1, 2, 3, or 4. Preferably, n is 0, 1, or 2.

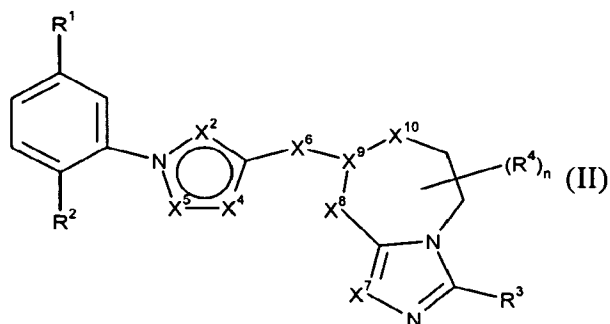
**[0064]** It is understood that the invention does not encompass the following compounds:

8-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine,

8-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-thiophen-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine,  
8-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine,  
8-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-{1-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-[5-(5-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-furan-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
3-Pyridin-4-yl-8-[1-(5-m-tolyl-[1,2,4]oxadiazol-3-yl)-ethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
(+)-8-{(1S)-1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidine,  
(-)-8-{(1R)-1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidine,  
3-[5-(3-Pyridin-4-yl-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl)[1,3,4]oxadiazol-2-yl]benzonitrile,  
3-{5-[3-(2-Methoxypyridin-4-yl)-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl][1,3,4]oxadiazol-2-yl}benzonitrile,  
3-{5-[3-(2-Methoxy-pyridin-4-yl)-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl]-[1,2,4]oxadiazol-3-yl}-benzonitrile,  
3-{3-[(3-pyridin-4-yl-6,7-dihydro[1,2,4]triazolo[4,3-a]pyrimidin-8(5H)-yl)methyl]-1,2,4-oxadiazol-5-yl}benzonitrile,

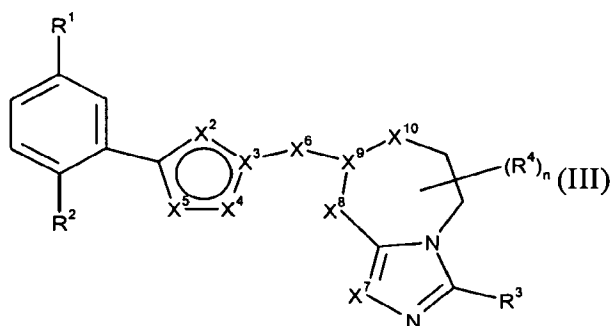
3-(3-{[3-(2-methoxypyridin-4-yl)-6,7-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidin-8(5*H*)-yl]methyl}-1,2,4-oxadiazol-5-yl)benzonitrile,  
 3-{5-[(3-pyridin-4-yl-6,7-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidin-8(5*H*)-yl)methyl]-1,2,4-oxadiazol-3-yl} benzonitrile, and  
 3-{5-[3-(2-Hydroxy-pyridin-4-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[4,3-*a*]pyrimidin-8-ylmethyl]-[1,2,4]oxadiazol-3-yl}-benzonitrile.

[0065] A subset of preferred compounds correspond to formula II:



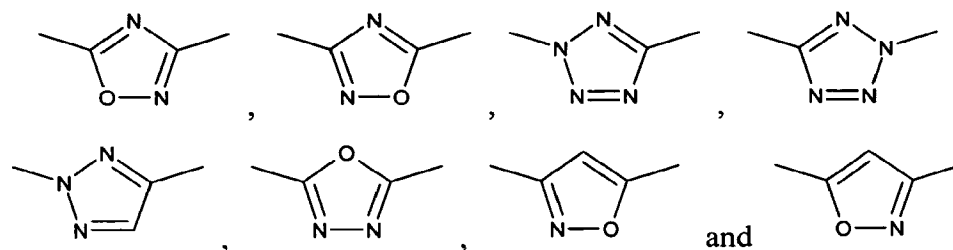
[0066] In formula II, the structural variables are as defined in formula I. In this context,  $X^7$  preferably is N.

[0067] Another subset of preferred compounds correspond to formula III:

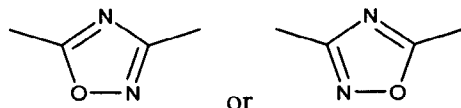


[0068] In formula III, the structural variables are as defined in formula I. Preferably,  $X^3$  is C or N.

[0069] In other embodiments of the invention, the ring containing  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , and  $X^5$  is selected from the group consisting of:



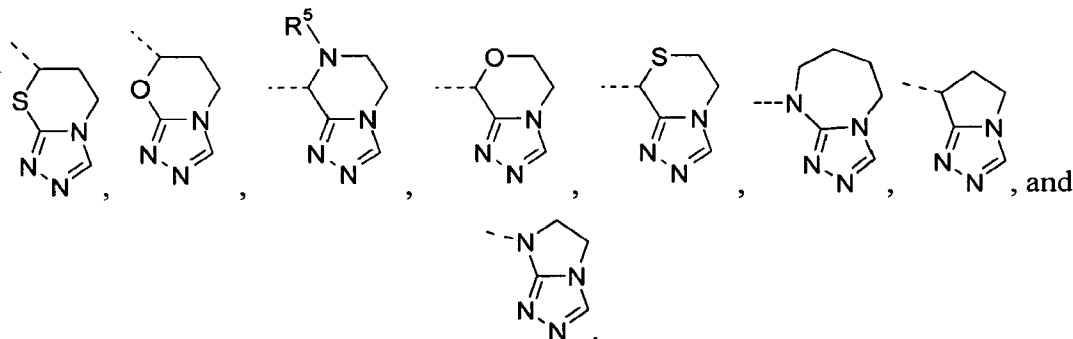
Preferably, the ring is either:



[0070] In these embodiments,  $X^7$  preferably is N, while  $X^8$  is preferably a bond. In one subset of compounds,  $X^9$  is  $CR^5$ , and  $X^{10}$  is  $NR^5$ , O,  $CR^5R^6$ , or  $(CR^5R^6)_2$ .

[0071] In another subset of compounds,  $X^8$  is preferably S. In this scenario,  $X^9$  preferably is  $CR^5$ , while  $X^{10}$  is a bond. In other embodiments,  $X^9$  is N.

[0072] In yet other embodiments of the invention, the fused ring containing  $X^7$ ,  $X^8$ ,  $X^9$ , and  $X^{10}$  is selected from the group consisting of:



[0073] Certain other embodiments of the invention are represented by the following exemplary compounds:

7-[5-(5-Chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-3-(2-thienyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3]thiazine,

9-[[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl]-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine,

9-{1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine,

7-[[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl]-3-pyridin-4-yl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole,

9- {[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine,  
8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine,  
8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-7-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and  
pharmaceutically acceptable salts thereof.

**[0074]** Embodiments of the invention include salt forms of the compounds of Formula I. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of Formula I.

**[0075]** A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

**[0076]** Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18<sup>th</sup> Edition, Mack Publishing Co.) 1990.

**[0077]** Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

**[0078]** The invention also relates to any and all tautomeric forms of the compounds of Formula I.

**[0079]** The invention further relates to hydrate and solvate forms of the compounds of Formula I.

#### **Pharmaceutical composition**

**[0080]** According to one aspect of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound of Formula I, or salts, solvates or solvated salts

thereof, in association with one or more pharmaceutically acceptable diluent, excipients and/or inert carrier.

[0081] The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

[0082] In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

[0083] Suitable daily doses of the compounds of formula I in the treatment of a mammal, including man are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration.

[0084] The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

### **Medical use**

[0085] It has been found that the compounds according to the present invention, exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor (mGluR) subtypes. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of mGluR5 and for inhibiting neuronal damage caused by excitatory activation of mGluR5. The compounds may be used to produce an inhibitory effect of mGluR5 in mammals, including man.

[0086] The mGluR Group I receptor including mGluR5 are highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of mGluR5-mediated disorders such as acute and chronic neurological and psychiatric disorders, gastrointestinal disorders, and chronic and acute pain disorders.

**[0087]** The invention relates to compounds of Formula I, as defined hereinbefore, for use in therapy.

**[0088]** The invention relates to compounds of Formula I, as defined hereinbefore, for use in treatment of mGluR5-mediated disorders.

**[0089]** The invention relates to compounds of Formula I, as defined hereinbefore, for use in treatment of Alzheimer's disease senile dementia, AIDS-induced dementia, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's Chorea, migraine, epilepsy, schizophrenia, depression, anxiety, acute anxiety, ophthalmological disorders such as retinopathies, diabetic retinopathies, glaucoma, auditory neuropathic disorders such as tinnitus, chemotherapy induced neuropathies, post-herpetic neuralgia and trigeminal neuralgia, tolerance, dependency, Fragile X, autism, mental retardation, schizophrenia and Down's Syndrome.

**[0090]** The invention relates to compounds of Formula I, as defined hereinbefore, for use in treatment of pain related to migraine, inflammatory pain, neuropathic pain disorders such as diabetic neuropathies, arthritis and rheumatoid diseases, low back pain, post-operative pain and pain associated with various conditions including angina, renal or biliary colic, menstruation, migraine and gout.

**[0091]** The invention relates to compounds of Formula I as defined hereinbefore, for use in treatment of stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, cardiovascular diseases and epilepsy.

**[0092]** The present invention relates also to the use of a compound of Formula I as defined hereinbefore, in the manufacture of a medicament for the treatment of mGluR Group I receptor-mediated disorders and any disorder listed above.

**[0093]** One embodiment of the invention relates to the use of a compound according to Formula I in the treatment of gastrointestinal disorders.

**[0094]** Another embodiment of the invention relates to the use of a compound according to Formula I, for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations, for the treatment of GERD, for the prevention of G.I. reflux, for the treatment regurgitation, treatment of asthma, treatment of laryngitis, treatment of lung disease and for the management of failure to thrive.



[0095] The invention also provides a method of treatment of mGluR5-mediated disorders and any disorder listed above, in a patient suffering from, or at risk of, said condition, which comprises administering to the patient an effective amount of a compound of Formula I, as hereinbefore defined.

[0096] The dose required for the therapeutic or preventive treatment of a particular disorder will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

[0097] In the context of the present specification, the term "therapy" and "treatment" includes prevention or prophylaxis, unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

[0098] In this specification, unless stated otherwise, the term "antagonist" and "inhibitor" shall mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

[0099] The term "disorder", unless stated otherwise, means any condition and disease associated with metabotropic glutamate receptor activity.

#### **Non- Medical use**

[0100] In addition to their use in therapeutic medicine, the compounds of Formula I, salts or hydrates thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of mGluR related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

#### **Methods of Preparation**

[0101] Another aspect of the present invention provides processes for preparing compounds of Formula I, or salts or hydrates thereof. Processes for the preparation of the compounds in the present invention are described herein.

[0102] Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily

understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to the one skilled in the art of organic synthesis. Examples of transformations are given below, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions on other suitable transformations are given in "Comprehensive Organic Transformations – A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by the one skilled in the art. The definitions of substituents and groups are as in formula I except where defined differently. The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

**[0103]** The term "reflux" shall mean, unless otherwise stated, in reference to an employed solvent a temperature at or above the boiling point of named solvent.

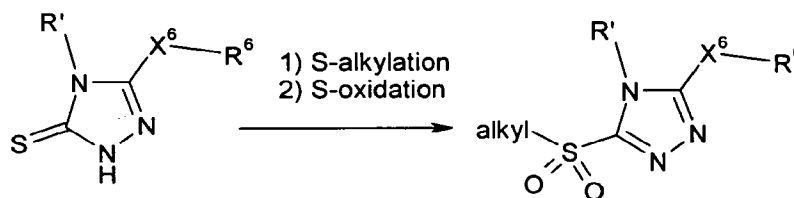
## [0104] Abbreviations

aq.	Aqueous
atm	atmosphere
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc, BOC	<i>tert</i> -butoxycarbonyl
CDI	N,N'-Carbonyldiimidazole
dba	Dibenzylideneacetone
DCC	N,N-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEA	N,N-Diisopropylethylamine
DIBAL-H	Diisobutylaluminum hydride
DIC	N,N'-Diisopropylcarbodiimide
DMAP	N,N-Dimethyl-4-aminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
EA or EtOAc	Ethyl acetate
EDC, EDCI	N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride
Et	Ethyl
Et <sub>2</sub> O	Diethyl ether
EtI	Iodoethane
EtOH	Ethanol
Et <sub>3</sub> N	Triethylamine
Fmoc, Fmoc	9-Fluorenylmethoxycarbonyl
h	hour(s)
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
Hep	heptane
Hex	hexane(s)
HetAr	Heteroaryl

HOBt	N-Hydroxybenzotriazole
HPLC	high performance liquid chromatography
LAH	lithium aluminum hydride
LCMS	HPLC mass spec
MCPBA	<i>m</i> -chlorbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeI	Iodomethane
MeMgCl	methyl magnesium chloride
MeOH	Methanol
min	Minutes
NaOAc	sodium acetate
<i>n</i> Bu	normal butyl
<i>n</i> BuLi, <i>n</i> -BuLi	1-butyllithium
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
o.n.	over night
OAc	acetate
OMs	mesylate or methane sulfonate ester
OTs	tosylate, toluene sulfonate or 4-methylbenzene sulfonate ester
PPTS	pyridinium <i>p</i> -toluenesulfonate
pTsOH	<i>p</i> -toluenesulfonic acid
RT, rt, r.t.	room temperature
sat.	Saturated
SPE	solid phase extraction
TBAF	tetrabutylammonium fluoride
tBu, t-Bu	<i>tert</i> -butyl
tBuOH, t-BuOH	<i>tert</i> -butanol
TEA	Triethylamine
THF	Tetrahydrofuran

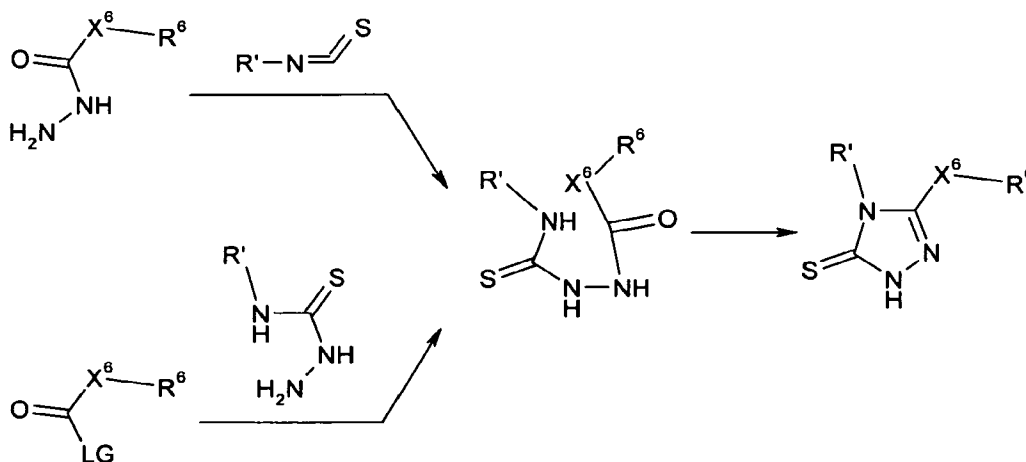
**Preparation of intermediates**

[0105] The compounds, and the corresponding intermediates throughout the non-limiting synthetic paths for which preparations are given below, are useful for further preparation of compounds of formula I or may represent the same. Other starting materials are either commercially available or can be prepared via methods described in the literature.

*[1,2,4]triazolethiones and Alkylsulphonyl[1,2,4]triazoles*

Scheme 1a

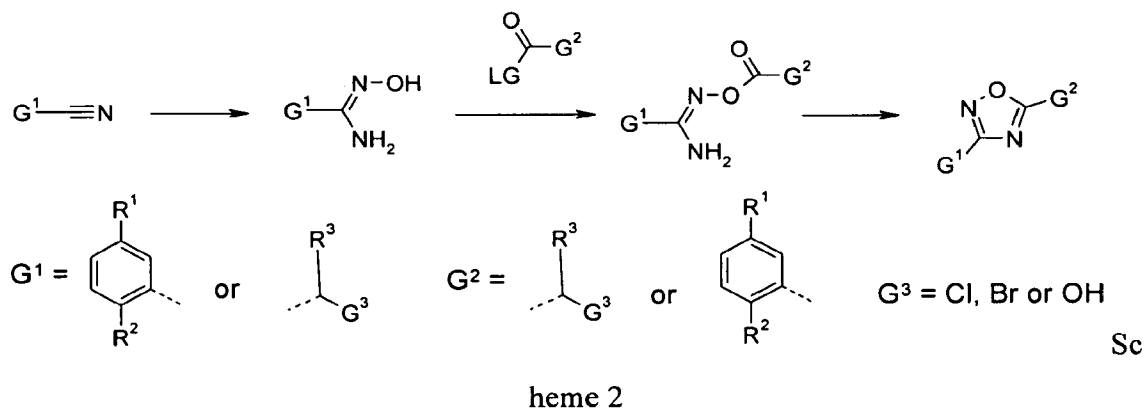
[0106] With reference to scheme 1a, alkylsulphonyl[1,2,4]triazoles can be prepared from the corresponding [1,2,4]triazolethiones by initial alkylation of the sulphur atom with primary alkyl halides such as MeI and EtI (alkyl is Me and Et respectively) in MeOH, EtOH, THF, acetone or the like at  $-30$  to  $100$  °C, followed by oxidation of the sulphur atom using for example  $\text{KMnO}_4$  in mixtures of water and acetic acid, or mCPBA in DCM, at  $-20$  to  $120$  °C, or by using any other suitable oxidant.



Scheme 1b

[0107] In reference to scheme 1b, [1,2,4]triazolethiones, wherein R' is a suitable side chain which may or may not be protected as appropriate, are for example prepared by N-acylation of a thiosemicarbazide, using any suitable acylating agent such as acid chlorides, bromides or fluorides (LG is Cl, Br or F) in for example pyridine, or acids (LG is OH), that are activated by the treatment with standard activating reagents as described herein below, in DMF, THF, DCM or the like at -20 to 120 °C, followed by ringclosure of the initially formed acyclic intermediate either spontaneously under the conditions of the acylation, or by heating at 50 to 150 °C in pyridine or in aqueous solvents in the presence of a base, such as NaHCO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub>, with or without co-solvents such as dioxane, THF, MeOH, EtOH or DMF. This acyclic intermediate can also be formed by treatment of the proper acyl hydrazide with a suitable isothiocyanate in for example 2-propanol, DCM, THF or the like at -20 to 120 °C.

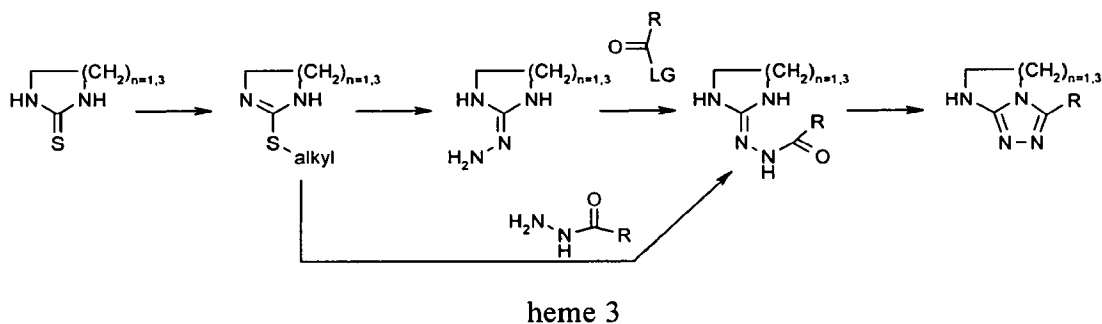
*[1,2,4]oxadiazoles*



[0108] With reference to scheme 2, [1,2,4]oxadiazoles with a carbon *alpha* to the heterocycle, wherein G<sup>1</sup>, G<sup>2</sup> and G<sup>3</sup> are defined as described in scheme 2, are formed by cyclization of G<sup>1</sup>- and G<sup>2</sup>-substituted-acyloxyimidamides in solvents such as pyridine, DMF, or water containing mixtures thereof, at 40 to 140 °C, alternatively in aqueous alcoholic solvents in the presence of sodium acetate at temperatures from 40 to 140 °C, with the later method being preferred if one of the groups G<sup>1</sup> or G<sup>2</sup> contains

a chiral stereocenter. Acyloxyimidamides are formed by coupling with a proper acylating agent carrying a leaving group LG with a G<sup>1</sup>-substituted hydroxamidine. The leaving group LG may be chloro or any other suitable leaving group as for example generated by *in situ* treatment of the corresponding acid (LG is OH) with standard activating reagents as described herein below. G<sup>1</sup>-substituted hydroxamidines are formed by reaction of the corresponding nitrile with the free base of hydroxylamine, or hydroxylamine hydrochloride in the presence of a base such as triethylamine, pyridine or sodium carbonate, in solvents such as ethanol, water or pyridine at temperatures from -20 to 120 °C

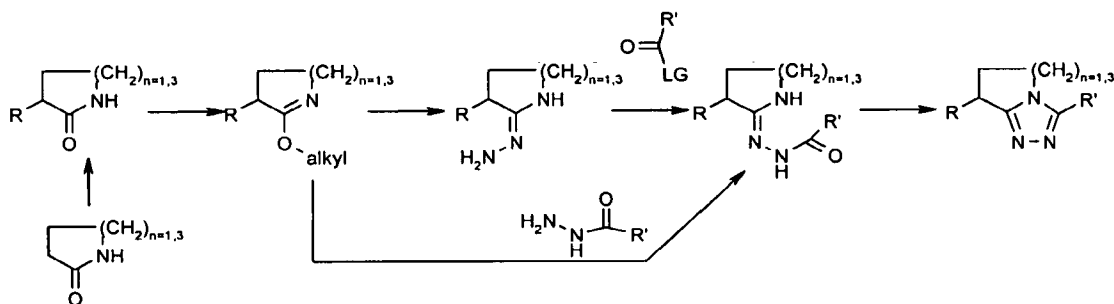
*Cyclic amino[1,2,4]triazoles*



[0109] With reference to scheme 3, cyclic amino[1,2,4]triazoles, wherein R is X<sup>6</sup>-R<sup>3</sup> as defined in formula I, are obtained by treating cyclic carbonyl-2-one hydrazones (e.g. 1,3-diazepan-2-one hydrazone for n=3 or the likes) with a proper acylating agent carrying a leaving group LG in suitable solvent such as THF, pyridine or DMF at -20 to 100 °C. The reaction initially leads to an open intermediate that either forms a triazole ring spontaneously, or can be made to do so by conventional, or microwave assisted, heating at 50 to 200 °C in for example pyridine or DMF. The leaving group LG may be chloro, bromo or fluoro (LG is Cl, Br or F), the corresponding anhydride (LG is O-C(=O)R) or any other suitable leaving group as for example generated by *in situ* treatment of the corresponding acid (LG is OH) with standard activating reagents as described herein above. Cyclic carbonyl-2-one hydrazones may be generated from isothioureas, in which the S-alkyl (for example S-Me or S-Et) moiety acts as a leaving group upon treatment with hydrazine in solvents such as pyridine, methanol, ethanol,

2-propanol, THF or the like at  $-20$  to  $180$  °C. The open intermediate can also be directly generated by treatment of isothioureas with acyl hydrazides under the same conditions as described for the reaction with hydrazine. Cyclic isothioureas are obtained by S-alkylation of the corresponding thioureas, which are commercially available or prepared according to standard procedures as known to the one skilled in the art, with for example MeI or EtI in acetone, EtOH, THF, DCM or the like at  $-100$  to  $100$  °C.

*Carbocyclic [1,2,4]triazoles*



S

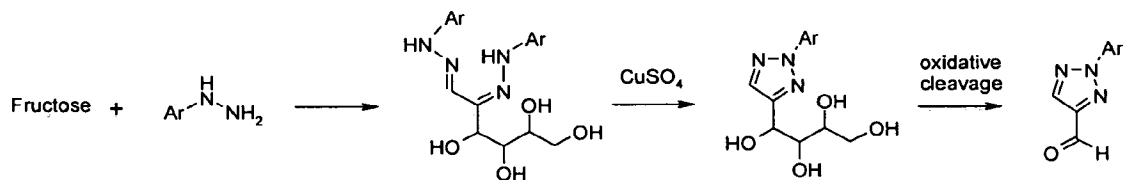
Scheme 4

[0110] With reference to scheme 4, wherein R either is H, or alkyl (Me, Et) and R' is  $X^6-R^3$  as defined in formula I, carbocyclic [1,2,4]triazoles are obtained by treating cyclic lactam hydrazones with a proper acylating agent to lead to an open chain intermediate which forms the triazole ring spontaneously or by heating as described herein above. Such cyclic lactam hydrazones are generated from the cyclic enol ether, in which the O-alkyl (alkyl is Me) moiety acts as a leaving group upon treatment with hydrazine as described herein above. Such open chain intermediates may also be formed directly by treatment of lactam enol ethers by treatment with acyl hydrazides as described herein above. Lactam enol ethers are prepared from their corresponding lactams by treatment with  $Me_3OBF_4$  or dimethylsulfate [Org.Preproced.Int;24, 1992, pp. 147-158 or Tetrahedron Lett. 42, 2001, pp. 173-1776]. R-substituted lactams are either commercially available or may be prepared by alkylation in the alpha position by treatment with 2 equivalents of a strong base such as n-BuLi followed by addition of 1 equivalent of alkylating agent, such as alkyl halide,



mesylate or triflate, in an aprotic solvents such as THF [J.Org. Chem. 64, 1999, pp. 6041-6048] or, alternatively, via a N-protected lactam, e.g. trimethylsilyl valerolactam or the likes, where only one equivalent of base is needed to generate the anion for alkylation [J.Org. Chem. 65, 2000, pp. 2684-2695]. The alkylation results in the formation of racemic product which may be separated into its enantiopure forms here, or at a later stage of the synthetic pathway by e.g. chiral chromatography.

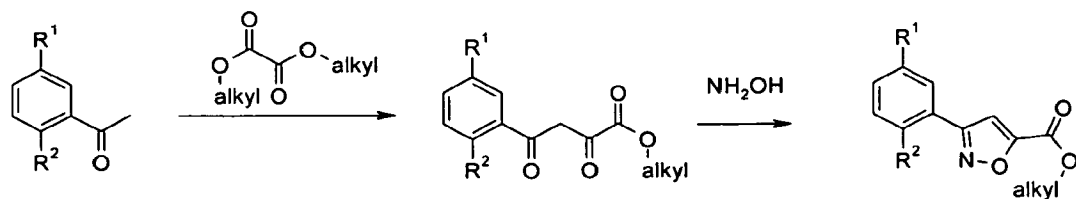
*2-Aryl-2H-[1,2,3]triazole-4-carbaldehydes*



Scheme 5

[0111] With reference to scheme 5, wherein Ar is 5-R<sup>1</sup>,2-R<sup>2</sup>-phenyl as defined in formula I, [1,2,3]triazole-4-carbaldehydes may be obtained from aryl glucosetriazoles by oxidative cleavage, employing for example periodic acid in aqueous mixtures of dioxane or THF at -20 to 120 °C. Aryl glucosetriazoles may be obtained by cyclization of the intermediate aryl glucosazone in the presence of copper (II) sulfate in aqueous mixtures of for example dioxane or THF at -20 to 120 °C. The aryl glucosazone in turn is made by coupling of arylhydrazines with fructose in acetic acid and water at -20 to 120 °C. [Buckler, R.; Hartzler, H.; Kurchacova, E.; Nichols, G.; Phillips, B.; J. Med. Chem.; 1978; 21(12); 1254-1260, and Riebsomer, J.; Sumrell, G.; J. Org. Chem.; 1948; 13(6); 807-814]

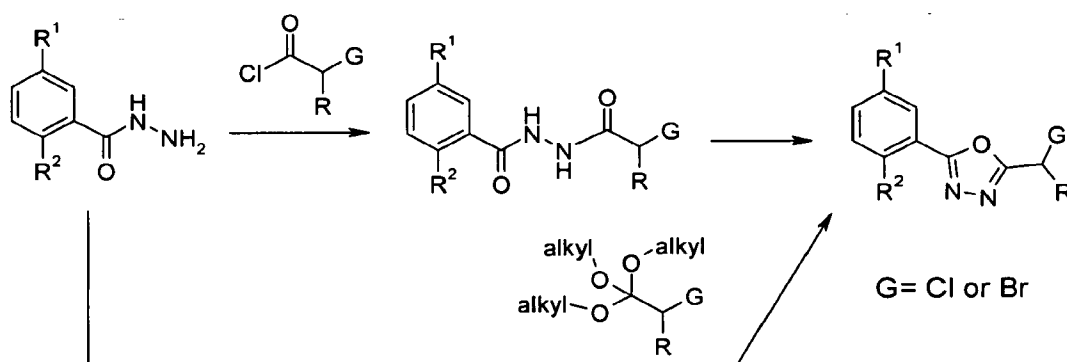
*Isoxazole-5-carboxylic acid esters*



Scheme 6

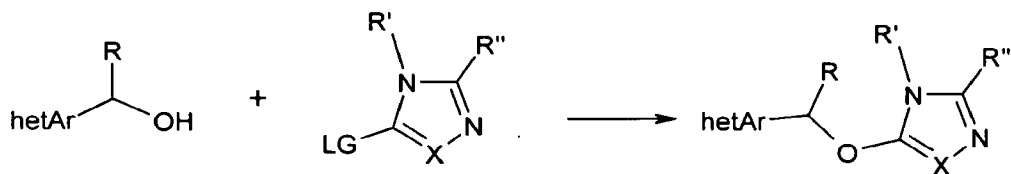
[0112] In reference to scheme 6, isoxazoles are formed by reaction and *in-situ* cyclization of dioxo butyric ester derivatives with hydroxylamine hydrochloride in solvents such as ethanol, 2-propanol or DMF at temperatures from 40 to 140 °C. Dioxo butyric esters are formed through the reaction of acetophenones with dialkyl oxolates (alkyl is for example Me or Et) in the presence of a strong base such as sodium hydride in solvents such as DMF or toluene at temperatures from -20 to 120 °C.

*[1,3,4]oxadiazoles*



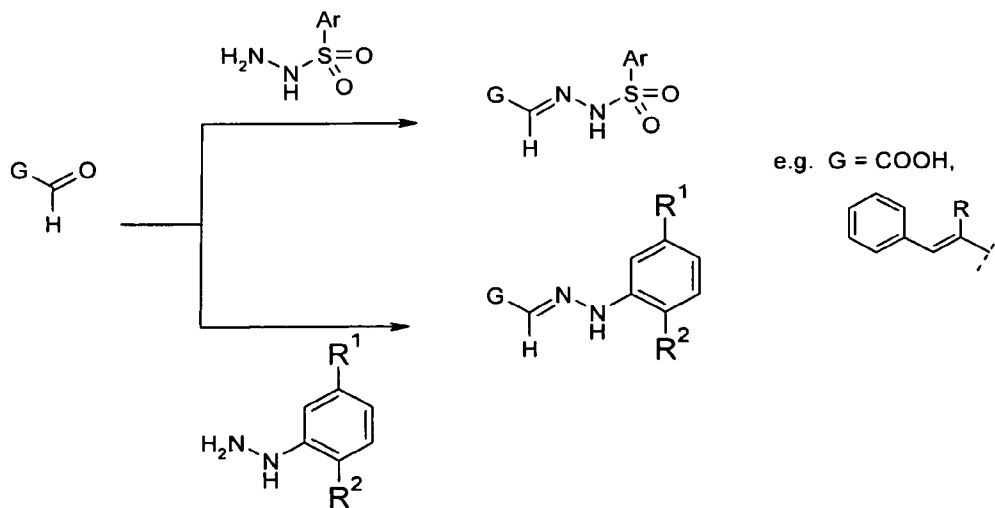
Scheme 7

[0113] With reference to scheme 7, wherein R is H or alkyl (Me, Et), starting from acid hydrazides, coupling with an aliphatic acid chloride derivative in THF, DMF, toluene or the like, optionally in the presence of a base such as triethylamine or a carbonate, leads to the formation of an acyl benzohydrazide derivative, which is cyclized at elevated temperatures in the presence of a dehydrating agent such as phosphorous pentoxide in solvents such as toluene or DMF or mixtures thereof to yield the [1,3,4]oxadiazole product. Alternatively, [1,3,4]oxadiazoles may be made directly from the acid hydrazide using trialkyl ortho esters either neat or in solvents such as toluene or xylenes at elevated temperatures.

*Triazole ethers*

Scheme 8

[0114] With reference to scheme 8, wherein R is H or alkyl (Me, Et), R' is a suitable side chain which may or may not be protected as appropriate, and R'' is X<sup>6</sup>-R<sup>3</sup> as defined in formula I, oxygen linked triazoles may be prepared by bond formation through nucleophilic replacement of a leaving group (LG) in which an alcohol acts as O-nucleophile under basic conditions. A base is used, for example, NaH or Cs<sub>2</sub>CO<sub>3</sub>, at temperatures from 0 to 80 °C in polar aprotic solvents such as DMF or acetonitrile. Examples of suitable leaving groups are alkylsulfonyls, such as methanesulfonyl and ethanesulfonyl, and halogens, such as chloro.

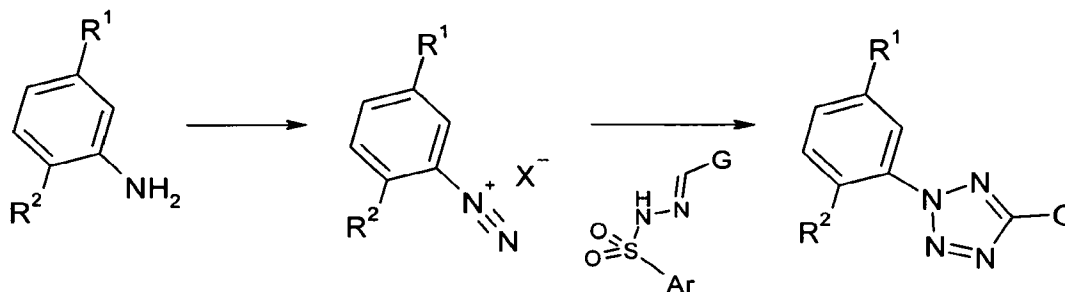
*Arylhydrazones and Arylsulfonylhydrazones*

Scheme 9

[0115] In reference to scheme 9, arylsulfonylhydrazones are prepared through condensation between aldehydes, for example cinnamaldehyde or glyoxalic acid, with

arylsulfonylhydrazines, such as 4-toluensulfonylhydrazine, in a suitable solvent, for example methanol, ethanol, DMF or dialkylethers, at a temperature between 0 to 100 °C, alternatively without solvent under microwave irradiation. Similarly, arylhydrazones may be formed from the reaction of arylhydrazines, with aldehydes. [J. Med. Chem. 1980, 23, 631-634; Monatshefte fuer Chemie 2001, 403-406; J. Med. Chem. 2000, 43, 953 – 970; J. Med Chem. 1978, 21, 1254-60]

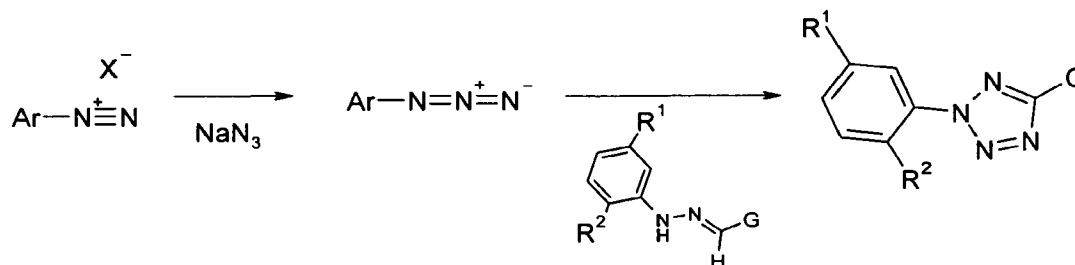
*Tetrazole formation*



Scheme 10a

[0116] In reference to scheme 10a, tetrazoles, wherein G is an electron withdrawing group, such as an olefin, carbonyl or aryl group, may be prepared by 1,3-dipolar cycloaddition of a diazonium salt onto an aryl sulfonyl hydrazone followed by elimination of the arylsulfinic acid to generate the tetrazole ring, in protic solvents such as water and alcohol or mixtures thereof, in basic aprotic solvents such as pyridine, or mixtures of these solvents with protic solvents used to generate the diazonium salt. [J. Med. Chem. 2000, 43, 953 – 970]. Diazonium salts in turn are available from a suitably substituted aryl or heteroaryl amine using well known methods, via diazotization using a nitrite source such as sodium nitrite or isoamyl nitrite in the presence of a suitable acid source such as hydrochloric acid or tetrafluoroboric acid in a solvent such as water at a temperature between -10 to 0 °C. In the case where a less soluble counterion X<sup>-</sup> is employed, such as tetrafluoroborate, the diazonium salt thus formed may be collected by precipitation and used in subsequent reactions under non-aqueous conditions. Soluble diazonium salts formed

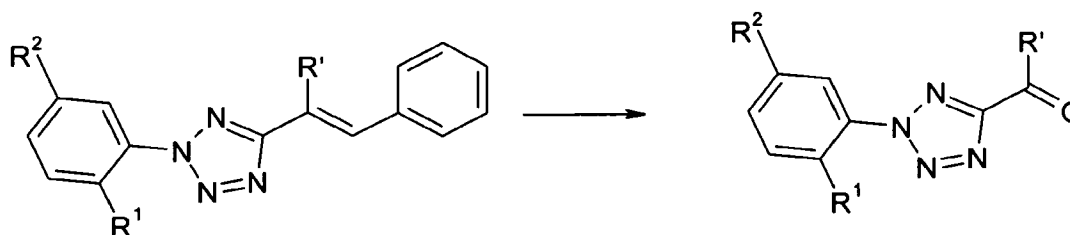
using other acid sources may be precipitated by the addition of a suitable reagent such as tetrafluoroboric acid or sodium tetrafluoroborate.



Scheme 10b

[0117] In reference to scheme 10b, tetrazoles may also be prepared from the reaction of an arylhydrazone, wherein G is defined as in scheme 9 and 10, with an aryl azide in a suitable solvent such as ethanol or pyridine. [J. Med Chem. 1978, 21, 1254-60] Aryl azides may be formed for example by using sodium azide with an aryl diazonium salt, which may in turn be prepared as described above from an aryl amine, for example aniline or 2,4,6-tribromoaniline. The aryl azide may be considered as a nitrogen transfer reagent since cycloaddition onto the hydrazone is followed by elimination to regenerate the aryl amine precursor to the diazonium salt.

*Preparation of 2-aryl tetrazole 5-carbonyls*

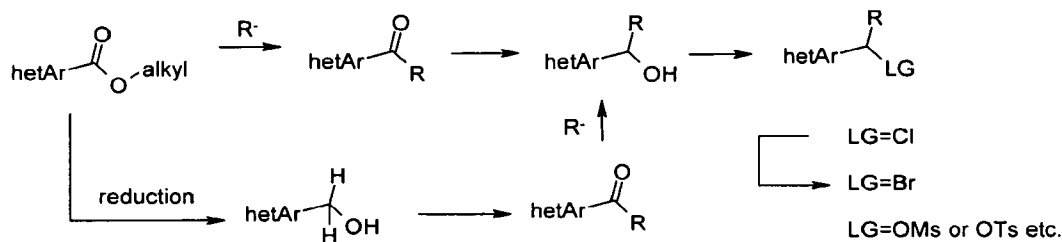


Scheme 11

[0118] Typically, G, as in reference to scheme 10a and 10b, is a group which may be employed as a precursor to the X<sup>6</sup> moiety in compounds of formula I, such as an olefin or carboxylic acid or acid derivative. With reference to scheme 11, when G is an aryl olefin, derived for example from cinnamaldehyde where R' is H, the olefin

group can be cleaved to provide an aldehyde directly in a one-pot process using a reagent such as ozone or via the diol using a dihydroxylation reagent such as osmium tetroxide as known by the one skilled in the art followed by subsequent cleavage using a reagent such as lead (IV) acetate. When a substituted cinnamaldehyde, such as  $\alpha$ -methylcinnamaldehyde wherein R' is methyl, is employed, a ketone would result from the cleavage of the olefin. [J.Med.Chem. 2000, 43, 953 – 970].

*Functional group transformations*



Scheme 12

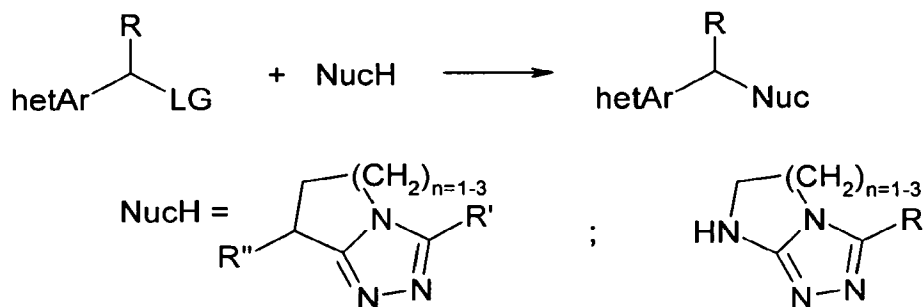
[0119] With reference to scheme 12, aliphatic alcohols may for example be converted by standard methods to the corresponding halides by the use of for example triphenylphosphine in combination with either iodine, N-bromosuccinimide or N-chlorosuccinimide, or alternatively by treatment with tribromophosphine or thionylchloride. Alcohols may be transformed to other leaving groups such as mesylates or tosylates by employing the appropriate sulfonyl halide or sulfonyl anhydride in the presence of a non-nucleophilic base together with the alcohol to obtain the corresponding sulphonates. Chlorides or sulphonates may be converted to the corresponding bromides or iodides by treatment with bromide salts, for example LiBr, or iodide salts, such as LiI. Further standard methods to obtain alcohols include the reduction of the corresponding carbonyl containing groups such as methyl or ethyl esters, aldehydes or ketones, by employing common reducing agents such as boranes, lithium borohydride, lithium aluminium hydride, or hydrogen in the presence of a transition metal catalyst such as complexes of for example ruthenium or iridium, or alternatively palladium on charcoal. Ketones and secondary alcohols may be obtained by treatment of carboxylic acid esters and aldehydes respectively, with the appropriate

carbon nucleophile, such as alkyl-Grignard reagents or alkyl-lithium reagents according to standard protocols. Heteroaromatic aldehydes may be prepared from the corresponding primary alcohols by oxidation procedures well known to the one skilled in the art, such as the employment of  $\text{MnO}_2$  as oxidant, or by Swern oxidation.

### **Preparation of final compounds**

[0120] The subsequent described non-limiting methods of preparation of final compounds are illustrated and exemplified by drawings in which the generic groups, or other structural elements of the intermediates correspond to those of formula I. It is to be understood that an intermediate containing any other generic group or structural element than those of formula I can be used in the exemplified reactions, provided that this group or element does not hinder the reaction and that it can be chemically converted to the corresponding group or element of formula I at a later stage which is known to the one skilled in the art.

*By nucleophilic intermolecular displacement*

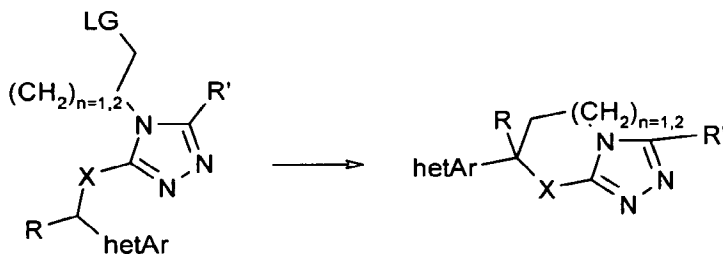


Scheme 13

[0121] With reference to scheme 13, wherein  $\text{R}''$  is H or alkyl (Me, Et), R is H or alkyl (Me, Et) and  $\text{R}'$  is  $\text{X}^6\text{-R}^3$  as defined in formula I, compounds of formula I can for example be prepared by bond formation through nucleophilic displacement of a leaving group (LG) in which the nucleophilic atom might be the amino-nitrogen atom of a heterocyclic amine, the alpha-carbon of an alkyl substituted heteroaromatic ring. Amino-nitrogen atoms of heterocyclic amines, and the alpha-carbons of alkyl substituted heteroaromatics, are generally not reactive in the neutral protonated form

and are therefore preferably fully or partly converted to more nucleophilic anionic forms by treatment with bases in suitable solvents such as LDA, HMDS-alkali, or *n*-BuLi in THF, diethylether or toluene, or NaH in for example DMF, or K<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> in acetonitrile or ketones such as 2-butanone, either *in situ* or just before the reaction with a suitable electrophile carrying a leaving group at a temperature from – 100 to 150 °C. The nitrogen atoms of secondary aliphatic amines are generally nucleophilic enough to displace a leaving group in the corresponding neutral forms, but preferably a base such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, TEA, DEA or the like is added to facilitate the reaction in solvents such as acetonitrile, DMF or DCM at 0 to 150 °C. For carbon nucleophiles, the leaving group is preferably bromo, for nitrogen nucleophiles examples of suitable leaving groups LG include chloro, bromo, OMs and OTs. Optionally, catalytic or stoichiometric amounts of an alkali metal iodide, such as LiI, can be present in the reaction to facilitate the same through in situ displacement of the leaving group to iodo.

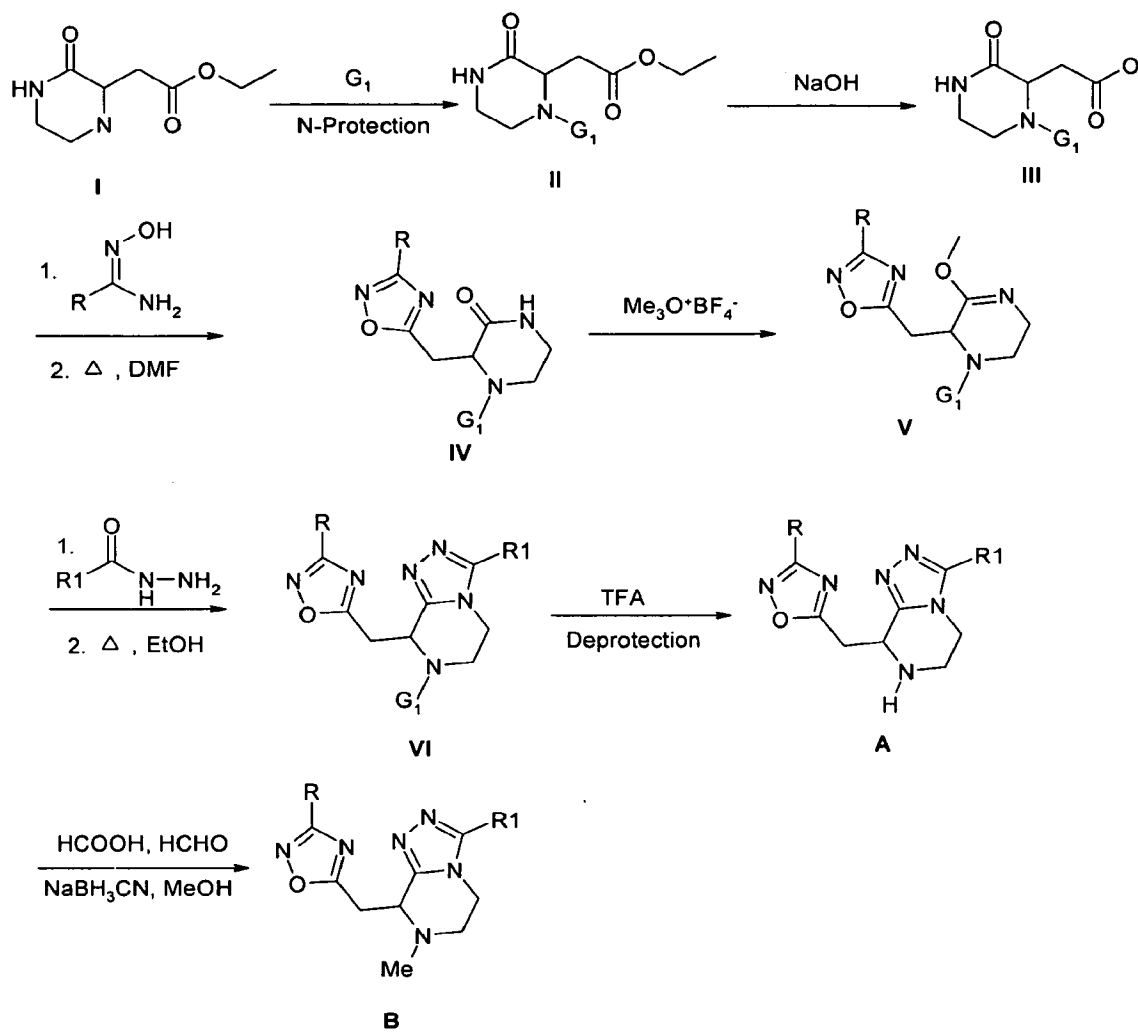
*By nucleophilic intramolecular displacement*



Scheme 14

[0122] With reference to scheme 14, wherein R is H or alkyl (Me, Et) and X is either S or O, compounds of formula I can for example be prepared by intramolecular bond formation through nucleophilic displacement of a leaving group (LG) in which the nucleophilic atom might be the the *alpha*-carbon of an alkyl substituted heteroaromate under conditions as described herein above for intermolecular displacements where preferred bases are for example LDA, HMDS-alkali, or NaH as described herein above.

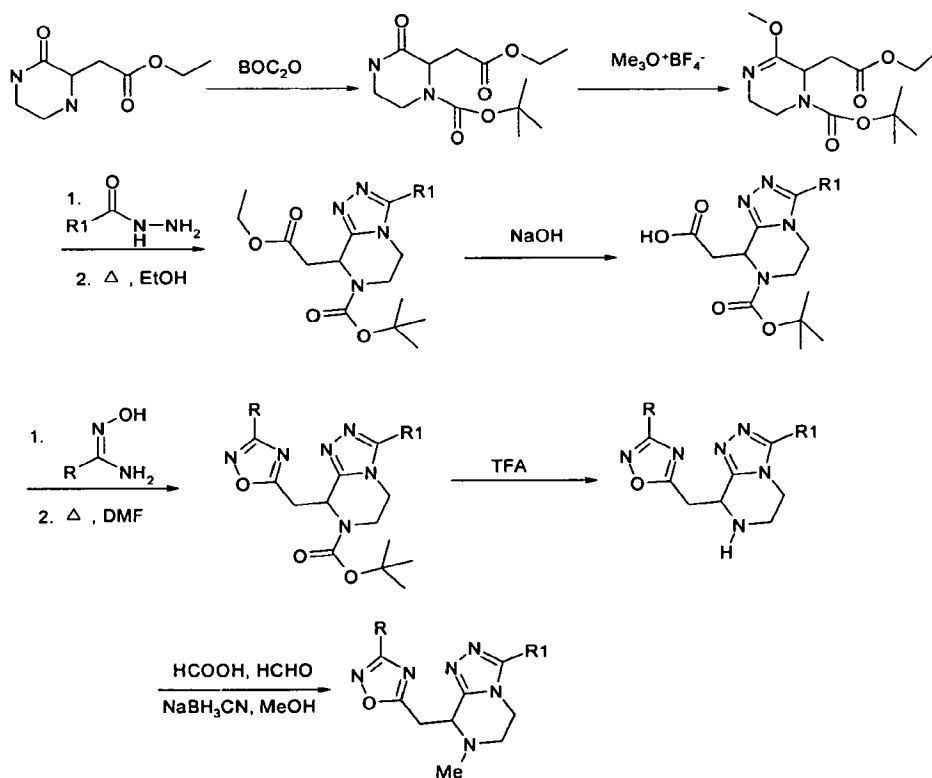


*Preparation of fused Piperazine-triazoles*

Scheme 15a

**[0123]** With reference to scheme 15a, the triazolopiperazines can be prepared from the piperazinone derivative by initial N-protection to give intermediate II. The intermediate can then be hydrolyzed to the acid III. The corresponding 1,2,4-oxadiazole IV can then be generated as described above. The triazolopiperazine intermediate VI can then be obtained by first converting IV to the cyclic imidoate, with a reagent such as  $\text{Me}_3\text{O}^+\text{BF}_4^-$  or dimethyl sulfate (ref: a) Sheu, Jennline; Smith, Michael B.; Oeschger, Thomas R.; Satchell, Jacqueline; Org.Prep.Proced.Int.; 24; 2; 1992; 147 – 158; b) Hutchinson, Ian S.; Matlin, Stephen A.; Mete, Antonio,

Tetrahedron Lett.; 42; 9; 2001; 1773 – 1776). The alkoxy group can then be displaced by an acyl hydrazide (or hydrazine with an acylating agent as described in Scheme 4) followed by a ring closing condensation to form the triazole heterocycle. This can be done in ethanol, toluene, DMF or pyridine under thermal conditions with regular heating or microwave irradiation (ref: Lawson, Edward C.; Hoekstra, William J.; Addo, Michael F.; Andrade-Gordon, Patricia; Damiano, Bruce P.; Kauffman, Jack A.; Mitchell, John A.; Maryanoff, Bruce E.; Bioorg.Med.Chem.Lett.; EN; 11; 19; 2001; 2619 – 2622). The protecting group can then be removed to afford compounds of formula A. Compound A can then be subjected to reductive alkylation to deliver compounds of formula B. Alternatively, compounds of formula A and B also be obtained according to the reaction sequence illustrated in Scheme 15b as shown below.



Scheme 15b

\* \* \* \* \*

[0124] The invention will now be illustrated by the following non-limiting examples.

**[0125] General methods**

[0126] All starting materials are commercially available or earlier described in the literature.

[0127] The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded either on Bruker 300, Bruker DPX400 or Varian +400 spectrometers operating at 300, 400 and 400 MHz for  $^1\text{H}$  NMR respectively, using TMS or the residual solvent signal as reference, in deuterated chloroform as solvent unless otherwise indicated. All reported chemical shifts are in ppm on the delta-scale, and the fine splitting of the signals as appearing in the recordings (s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet).

[0128] Analytical in line liquid chromatography separations followed by mass spectra detections, were recorded on a Waters LCMS consisting of an Alliance 2795 (LC) and a ZQ single quadropole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source operated in a positive and/or negative ion mode. The ion spray voltage was  $\pm 3$  kV and the mass spectrometer was scanned from m/z 100-700 at a scan time of 0.8 s. To the column, X-Terra MS, Waters, C8, 2.1 x 50mm, 3.5 mm, was applied a linear gradient from 5 % to 100% acetonitrile in 10 mM ammonium acetate (aq.), or in 0.1% TFA (aq.).

[0129] Preparative reversed phase chromatography was run on a Gilson autopreparative HPLC with a diode array detector using an XTerra MS C8, 19x300mm, 7mm as column.

[0130] Purification by a chromatotron was performed on rotating silica gel / gypsum (Merck, 60 PF-254 with calcium sulphate) coated glass sheets, with coating layer of 1, 2, or 4 mm using a TC Research 7924T chromatotron.

[0131] Purification of products were also done using Chem Elut Extraction Columns (Varian, cat #1219-8002), Mega BE-SI (Bond Elut Silica) SPE Columns

(Varian, cat # 12256018; 12256026; 12256034), or by flash chromatography in silica-filled glass columns.

**[0132]** Microwave heating was performed in a Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden).

### **Preparation of intermediates**

#### **[0133] Example 1**

**[0134]** **[3-(2-Thienyl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetic acid**

**[0135]** Methyl N-(thioxomethylene)glycinate (2.06 g) and thiophene-2-carbohydrazide (2.57 g) in isopropanol (50 ml) was heated at 70 °C while stirring for 16 h. The mixture was allowed to come to r.t. and the formed precipitate collected and heated at reflux in 1.0 M aqueous NaHCO<sub>3</sub> solution for 2 h. After cooling to r.t. and acidification with conc. HCl (aq.) the product was extracted into EA, which was washed with brine and then dried over MgSO<sub>4</sub> before concentration to dryness to yield crude title compound which was used directly in the next step.

#### **[0136] Example 2**

**[0137]** **4-(2-Hydroxyethyl)-5-(2-thienyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione**

**[0138]** All of the crude [3-(2-thienyl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetic acid from the previous step was dissolved in THF (20 ml). This solution was added dropwise at 0 °C to a slurry of LAH (2 g) in THF (80 ml) while stirring before allowed to come to r.t. for 2 h. The r.m. was then quenched with sat. Na<sub>2</sub>SO<sub>4</sub> (aq.) at 0 °C and the pH adjusted to 3-4 before filtration through celite. The THF was removed from the filtrate by concentration and the product extracted with EA from the remaining aq. mixture. The EA-phase was then washed with brine and dried over MgSO<sub>4</sub> before concentration to dryness to yield a crude material that was recrystallized from MeOH to provide 485 mg of the title compound. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 13.94 (br.s, 1H), 7.86 (d, 1H), 7.81 (d, 1H), 7.24 (dd, 1H), 5.09 (t, 1H), 4.16 (t, 2H), 3.76 (q, 2H)

**[0139] Example 3**

**[0140] 2-[3-([5-(5-Chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]methyl)thio]-5-(2-thienyl)-4H-1,2,4-triazol-4-yl]ethanol**

**[0141]** 4-(2-Hydroxyethyl)-5-(2-thienyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (101 mg), 5-(5-chloro-2-fluorophenyl)-3-(chloromethyl)-1,2,4-oxadiazole (116 mg), and potassium carbonate (86 mg) was stirred in a mixture of DMF (2 ml) and MeCN (15 ml) at r.t. for 3 h before concentration to dryness and washing of the residue with water, and then with EtOAc, to provide 122 mg of the title compound as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 8.04 (dd, 1H), 7.83 (m, 1H), 7.78 (d, 1H), 7.66 (d, 1H), 7.58 (t, 1H), 7.22 (dd, 1H), 5.16 (t, 1H), 4.59 (s, 2H), 4.18 (t, 2H), 3.64 (q, 2H)

**[0142] Example 4**

**[0143] 2-[3-([5-(5-Chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]methyl)thio]-5-(2-thienyl)-4H-1,2,4-triazol-4-yl]ethyl methanesulfonate**

**[0144]** To a solution of 2-[3-([5-(5-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]methyl)thio]-5-(2-thienyl)-4H-1,2,4-triazol-4-yl]ethanol in a mixture of DMF (1 ml) and pyridine (0.5 ml) was added methanesulfonyl chloride (20  $\mu$ L). The mixture was stirred at r.t. for 24 h before poured onto water (10 ml). The crude product was filtered off and purified by chromatography on silica gel using 0-5% MeOH in DCM as eluent to give 43 mg of the title compound, which was used directly in the next step.

**[0145] Example 5**

**[0146] 3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine**

**[0147]** A mixture of 1,3-diazepan-2-one hydrazone hydroiodide (1.00 g, 3.9 mmol) and isonicotinoyl chloride hydrochloride (695 mg, 3.9 mmol) was heated in a microwave reactor at 160 °C for 10 min. The reaction mixture was pured into Na<sub>2</sub>CO<sub>3</sub> solution, sat., and extracted with DCM. The organic phase was dried and concentrated. Flashchromatography (DCM/MeOH 20:1) gave 1.74 g crude title

compound which was used directly in the next step. <sup>1</sup>H NMR: 1.89 (s, 4 H), 3.15 (m, 2 H), 3.86 (m, 2 H), 7.44 (d, 2 H), 8.66 (d, 2 H).

**[0148] Example 6**

**[0149] 3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-*a*][1,3]diazepine**

**[0150]** Trifluoroacetic acid anhydride (0.24 ml, 1.71 mmol) was added to a solution of 1,3-diazepan-2-one hydrazone hydroiodide in DCM (10 ml). The reaction mixture was stirred for 24 h at r.t. The volatiles were removed and the residue was refluxed in aq. sat. NaHCO<sub>3</sub> for 2 h. After cooling to r.t. the product was collected by filtration, washed with water and dried to afford 101 mg (31%) of the title compound. <sup>1</sup>H NMR: 1.85 - 1.96 (m, 4 H), 3.17 (m, 2 H), 3.99 (m, 2 H), 5.04 (s, 1 H).

**[0151] Example 7**

**[0152] 1,3-diazepan-2-one hydrazone hydroiodide**

**[0153]** Hydrazine hydrate (0.44 ml, 7.23 mmol) was added to a solution of 2-(methylthio)-4,5,6,7-tetrahydro-1*H*-1,3-diazepine hydroiodide (1.79 g, 6.58 mmol) in EtOH (12 ml). The reaction mixture was refluxed for 5 h and cooled to r.t. Et<sub>2</sub>O was added and the product was collected by filtration, washed with Et<sub>2</sub>O and dried under vacuum to give 1.46 g (100%) crude title compound which was used directly in the next step.

**[0154] Example 8**

**[0155] 2-(methylthio)-4,5,6,7-tetrahydro-1*H*-1,3-diazepine**

**[0156]** Methyl iodide (0.55 ml, 1.15 mmol) was added to a solution of 1,3-diazepan-2-thione (1.00 g, 7.68 mmol) in acetone (8 ml). The reaction mixture was refluxed for 15 min. EtOH was added to the hot solution to dissolve the solids. After cooling to r.t. hex. was added and the precipitate was collected by filtration, washed with hex. and dried to give 1.79 g (86%) crude title compound which was used directly in the next step.

**[0157] Example 9****[0158] 3-pyridin-4-yl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole**

**[0159]** Me<sub>3</sub>OBF<sub>4</sub> (2.66 g, 18 mmol) was added to a solution of 2-pyrrolidinone in DCM (150 ml) and the reaction mixture was stirred for 24 h. The reaction mixture was washed with aq. sat. NaHCO<sub>3</sub>, dried and concentrated. The residue was dissolved in EtOH (4 ml) and isonicotinic hydrazide (1.37 g, 10 mmol) was added. The mixture was heated in a microwave reactor for 1 h at 120 °C. The volatiles were removed and the crude product purified with column chromatography (DCM/MeOH 20:1) to give 319 mg (11%) of the title compound. <sup>1</sup>H NMR: 2.87 (m, 2 H), 3.05 (t, 2 H), 4.28 (t, 2 H), 7.72 (d, 2 H), 8.72 (d, 2 H).

**[0160] Example 10****[0161] 3-Chloromethyl-5-(3-chloro-phenyl)-1,2,4-oxadiazole**

**[0162]** Step A. The acyclic intermediate was obtained from 3-chlorobenzoic acid (2.82 g, 18 mmol), EDCI (3.46 g, 18 mmol), HOBt (2.76 g, 18 mmol) and 2-chloro-N-hydroxy-acetamidine (1.75 g, 16.2 mmol) [Chem. Ber. 1907, 40, 1639] in DMF (40 mL). Step B: The cyclic compound was obtained from heating in DMF (40 mL) and purified by SPE chromatography on silica gel using 2% acetone in hex.s yielded the title compound (1.46 g, 39% yield over 2 steps). <sup>1</sup>H NMR: 8.17 (m, 1H), 8.07 (dd, 1H), 7.60 (m, 1H), 7.55 (t, 1H), 4.69 (s, 2H).

**[0163] Example 11****[0164] 3-(Bromomethyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole**

**[0165]** 3-(chloromethyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole (1.38 g, 6.0 mmol) and LiBr (0.90 g, 10.3 mmol) in THF (50 ml) was heated to reflux under a nitrogen atmosphere o.n. After cooling to r.t. EA was added and the organic phase was washed with H<sub>2</sub>O and brine, dried and evaporated to give the title compound (1.40 g, 85%). MS (M<sup>+</sup>+1) 275

**[0166] Example 12****[0167] 3-(1-chloroethyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole**

**[0168]** 5 drops of DMF was added to 1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethanol (12.3 g, 54.9 mmol) in SOCl<sub>2</sub> (150 mL) and the reaction was heated at 70 °C for 5 h. The excess SOCl<sub>2</sub> was evaporated and the residue was purified by column chromatography (Hep to Hep-EA 5:1) to give 12.4 g (93 %) of the title compound. <sup>1</sup>H NMR: 1.96 (d, 3H) 5.20 (q, 1H) 7.46 (t, 1H) 7.59 (m, 1H) 8.04 (m, 1H) 8.17 (t, 1H)

**[0169] Example 13****[0170] 1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl methanesulfonate**

**[0171]** Methane sulfonyl chloride (40 µl, 0.49 mmol) was added to a mixture of TEA (95 µl, 0.67 mmol) and 1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethanol (100 mg, 0.45 mmol) in DCM (5 ml). After stirring for 15 min the mixture was washed with water and brine, dried and concentrated and the title compound was obtained in 135 mg yield. <sup>1</sup>H NMR: 1.9 (d, 3 H), 3.1 (s, 3 H), 5.9 (q, 1 H), 7.5 (t, 1 H), 7.6 (m, 1 H), 8.0 (m, 1 H), 8.1 (t, 1 H)

**[0172] Example 14****[0173] 1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethanol**

**[0174]** 27.2 g crude N'-[(3-chlorobenzoyl)oxy]-2-hydroxypropanimidamide was dissolved in ethanol (250 mL) and refluxed for 1 h, followed by addition of 14.0 g (170 mmol) sodium acetate in water (40 mL). After refluxing o.n., cooling to r.t. and addition of water (250 mL) the mixture was concentrated *in vacuo* to about ½ of its volume, resulting in a precipitate which was filtered off and recrystallized from EA/Hep to yield 6.45 g (25%) of the title compound. <sup>1</sup>H NMR: 8.14 (s, 1 H), 8.02 (d, 1 H), 7.57 (d, 1 H), 7.47 (t, 1 H), 5.04 - 5.14 (m, 1 H), 2.51 (d, 1 H), 1.67 (d, 3 H)

**[0175] Example 15****[0176] N'-[(3-chlorobenzoyl)oxy]-2-hydroxypropanimidamide**

**[0177]** 6.45 g crude N',2-dihydroxypropanimidamide was cooled on an ice-bath with 23.5 mL DEA in THF (200 mL). To this slurry 21.94 g 3-chlorobenzoyl chloride



was added. The mixture was warmed to r.t. and stirred for 2 h. Addition of Et<sub>2</sub>O (200 mL), washing with sat. aq. NH<sub>4</sub>Cl and re-extraction of the aq. layer gave after combining and concentration of the org. layers followed by drying *in vacuo* 27.24 g of crude title compound, which was directly used in the next step. LC-MS (M<sup>+</sup>+1): 243.

**[0178] Example 16**

**[0179] N',2-dihydroxypropanimidamide**

**[0180]** 44.2 g (0.64 mol) of hydroxylamine hydrochloride and 25.5 g (0.64 mol) sodium hydroxide were dissolved in ethanol (500 mL) at r.t. and stirred for 3 h. After filtration, 8.11 g (0.11 mol) 2-hydroxypropanenitrile were added to the filtrate, followed by stirring for 4 h. After concentration to dryness the title compound was obtained which was directly used in the next step. <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): 8.88 (s, 1 H), 5.15 (s, 1 H), 5.02 (s, 1 H), 4.00 (q, 1 H), 1.19 (d, 3 H).

**[0181] Example 17**

**[0182] 2-Ethoxycarbonylmethyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester**

**[0183]** Triethyl amine (9.0 mL, 64.4 mmol) and di-*tert*-butyl-dicarbonate (7.0 g, 32.2 mmol) were added to (3-oxo-piperazin-2-yl)-acetic acid ethyl ester (4.0 g, 21.5 mmol) in 1,4-dioxane (4.0 mL) and water (2 mL) at room temperature and stirred overnight. The reaction mixture was concentrated and then the residue was diluted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was triturated with hexanes, filtered, and dried to afford the titled compound (5.66 g, 92%, white solid). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 6.29 (bs, 1H), 4.78 (m, 1H), 4.16 (m, 3H), 3.40 (m, 3H), 2.99 (m, 1H), 2.90 (m, 1H), 1.50 (s, 9H), 1.28 (t, 3H).

**[0184] Example 18**

**[0185] 2-Carboxymethyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester**

**[0186]** 1N Sodium hydroxide (11.4 mL, 11.4 mmol) was added to 2-ethoxycarbonylmethyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (2.5 g, 8.73

mmol) in methanol (20 mL) at room temperature and then stirred for 2.5 hours. The reaction mixture was concentrated, acidified with 2N HCl to pH~2 and extracted with dichloromethane (3 times). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the titled compound (1.87 g, 83%, white foam solid). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 7.68 (bs, 1H), 4.78 (m, 1H), 4.19 (m, 1H), 3.45 (m, 1H), 3.34 (m, 2H), 2.97 (m, 2H), 1.49 (s, 9H).

**[0187] Example 19**

**[0188] 2-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester**

**[0189]** 2-Carboxymethyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.87 g, 7.25 mmol), 3-chloro-N-hydroxy-benzamidine (1.36 g, 7.98 mmol), HOBt (1.08 g, 7.98 mmol) and EDCI (1.53 g, 7.98 mmol) in DMF (20 mL) were stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water (3 times), saturated sodium bicarbonate (2 times) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in DMF (20 mL) and then heated at 135°C for 4 hours. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water (3 times) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification was performed by flash chromatography on silica gel using hexanes:dichloromethane (1:1) to afford the titled compound (1.48 g, 52%, white foam solid). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.08 (m, 1H), 7.97 (m, 1H), 7.46 (m, 2H), 6.35 (m, 1H), 5.04 (m, 1H), 4.31 (m, 1H), 3.68 (m, 1H), 3.50 (m, 2H), 3.27 (m, 2H), 1.35 (bs, 9H).

**[0190] Example 20**

**[0191] 6-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-5-methoxy-3,6-dihydro-2H-pyrazine-1-carboxylic acid tert-butyl ester**

**[0192]** Trimethyloxonium tetrafluoroborate (169.4 mg, 1.15 mmol) was added to 2-[3-(3-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (450 mg, 1.15 mmol) in dichloromethane (3 mL) under argon at room temperature and then stirred overnight. The reaction mixture was directly purified by

flash chromatography on basic alumina using 30 % ethyl acetate in hexanes to afford the titled compound (284.6 mg, 61%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.09 (m, 1H), 7.97 (m, 1H), 7.46 (m, 2H), 4.88 (m, 1H), 4.01 (m, 1H), 3.72 (s, 3H), 3.51 (m, 3H), 3.35 (m, 1H), 2.90 (m, 1H), 1.34 (m, 9H).

**[0193] Example 21**

**[0194] 8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carboxylic acid tert-butyl ester**

**[0195]** 6-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-5-methoxy-3,6-dihydro-2H-pyrazine-1-carboxylic acid tert-butyl ester (284.6 mg, 0.70 mmol) and 4-methoxy-benzoic acid hydrazide (116.2 mg, 0.70 mmol) under argon in methanol (10 mL) were heated at reflux for 3 days. After cooling, the reaction mixture was diluted with ethyl acetate and then washed with water (3 times) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel using 40 – 85 % ethyl acetate in hexanes afforded the titled compound (72.5 mg, 20%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.07 (m, 1H), 7.96 (m, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.05 (m, 2H), 6.04 (m, 1H), 4.11 (m, 2H), 3.89 (s, 3H), 3.86 (m, 2H), 3.55 (m, 1H), 3.31 (m, 1H), 1.28 (bs, 9H).

**Preparation of final compounds**

**[0196] Example 22**

**[0197] 7-[5-(5-Chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-3-(2-thienyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3]thiazine**

**[0198]** To a solution of 2-[3-({[5-(5-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]methyl}thio)-5-(2-thienyl)-4H-1,2,4-triazol-4-yl]ethyl methanesulfonate (43 mg) in DMF (2 ml) was added sodium hydride (10 mg) at – 78 °C while stirring. The mixture was allowed to come to r.t. and stirred for another 3 h before addition of MeOH (1 ml) and concentration onto silica gel. Purification by chromatography on silica gel using DCM:EA:MeOH 70:30:2 as eluent provided 2.8 mg of the title compound. <sup>1</sup>H

NMR: 8.07 (dd, 1H), 7.56 (m, 1H), 7.51 (dd, 1H), 7.47 (dd, 1H), 7.17-7.23 (m, 2H), 4.86 (dd, 1H), 4.60 (m, 1H), 4.38 (m, 1H), 2.82 (m, 2H)

**[0199] Example 23**

**[0200] 9-{[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine**

**[0201]** NaH (65 mg, 0.28 mmol) was added to a solution of 3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine (54 mg, 0.25 mmol) in DMF (5 ml). After 10 min 3-(chloromethyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole (65 mg, 0.28 mmol) was added at r.t. Stirring was continued o.n. and NH<sub>4</sub>Cl solution, sat., was added and the mixture was extracted with EA. The organic phase was dried and concentrated. Flashchromatography (DCM/MeOH 20:1) yielded 56 mg (54%) of the title compound. <sup>1</sup>H NMR: 1.89 - 2.01 (m, 4 H), 3.33 - 3.42 (m, 2 H), 3.90 - 3.98 (m, 2 H), 4.88 (s, 2 H), 7.42 - 7.49 (m, 3 H), 7.53 (m, 1 H), 7.98 (m, 1 H), 8.09 (m, 1 H), 8.71 (d, 2 H).

**[0202] Example 24**

**[0203] 9-{1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine**

**[0204]** The title compound was prepared analogous to 9-{[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine from 1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl methanesulfonate (186 mg, 0.61 mmol), 3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine (200 mg, 0.56 mmol) to give 8.1 mg (4%) of the title compound. <sup>1</sup>H NMR: 1.83 (d, 3 H), 1.86 - 1.95 (m, 4 H), 3.16 - 3.27 (m, 1 H), 3.43 - 3.53 (m, 1 H), 3.75 - 3.87 (m, 1 H), 3.95 - 4.07 (m, 1 H), 5.54 (q, 1 H), 7.41 - 7.52 (m, 3 H), 7.52 - 7.58 (m, 1 H), 8.01 (m, 1 H), 8.12 (m, 1 H), 8.73 (m, 2 H).

**[0205] Example 25**

**[0206] 7-{{5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl}methyl}-3-pyridin-4-yl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole**

**[0207]** nBuLi (2.5 M, hex., 600 µl) was added to a solution of 3-pyridin-4-yl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole (250 mg, 1.33 mmol) in THF (13 ml) at 0 °C. After 10 min the reaction mixture was cooled to -78 °C and 3-(bromomethyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole (400 mg, 1.46 mmol) in THF (10 ml) was added. After stirring at -78 °C for 30 min stirring was continued at 0 °C reaching r.t. o.n.. Aq. sat. NH<sub>4</sub>Cl was added and the mixture was extracted with EA. The organic phase was washed with water and brine, dried and concentrated. Flashchromatography (DCM/MeOH 40:1) followed by preparative HPLC afforded 6.5 mg (1%) of the title compound. <sup>1</sup>H NMR: 2.72 (m, 1 H), 3.13 (m, 2 H), 3.62 (m, 1 H), 3.93 (m, 1 H), 4.31 (m, 2 H), 7.47 (t, 1 H), 7.56 (m, 1 H), 7.74 (d, 2 H), 7.98 (m, 1 H), 8.08 (m, 1 H), 8.74 (m, 2 H).

**[0208] Example 26**

**[0209] 9-{{5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl}methyl}-3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine**

**[0210]** The title compound was prepared analogous to 9-{{5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl}methyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine from 3-(chloromethyl)-5-(3-chlorophenyl)-1,2,4-oxadiazole (89 mg, 0.39 mmol), 3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine (73 mg, 0.35 mmol. Column chromatography (hep./EA 1:1) afforded 85 mg (61%) of the title compound. <sup>1</sup>H NMR: 1.88 (m, 2 H), 1.94 (m, 2 H), 3.26 - 3.35 (m, 2 H), 3.98 - 4.07 (m, 2 H), 4.83 (s, 2 H), 7.46 (m, 1 H), 7.50 - 7.57 (m, 1 H), 7.98 (m, 1 H), 8.09 (m, 1 H)

**[0211] Example 27****[0212] 8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine**

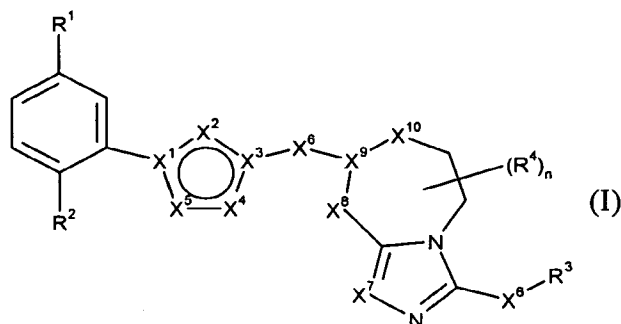
**[0213]** Trifluoroacetic acid (0.5mL) was added to a solution of 8-[3-(3-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carboxylic acid tert-butyl ester (72.5 mg, 0.14 mmol) in dichloromethane (1 mL) at 0°C. The reaction mixture was then diluted with dichloromethane, After 15 minutes, the reaction was warmed to room temperature and stirred for an additional hour. washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated. Purification was performed by flash column chromatography on silica gel using 85 – 90% ethyl acetate in hexanes to 2% ammonia in methanol in dichloromethane followed by trituration with diethyl ether to afford the titled compound (40.6 mg, 69%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.10 (m, 1H), 8.00 (m, 1H), 7.67 (m, 2H), 7.48 (m, 2H), 7.05 (m, 2H), 7.86 (m, 1H), 4.09 (m, 3H), 3.89 (s, 3H), 3.47 (m, 2H), 3.24 (m, 1H), 2.83 (bs, 1H).

**[0214] Example 28****[0215] 8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-7-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine**

**[0216]** Formic acid (0.1 mL), formaldehyde (37 wt. % solution in water, 0.1 mL) and sodium cyanoborohydride (1.0 M in THF, 0.1 mL) were added to a solution of 8-[3-(3-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (30 mg, 0.071 mmol) in methanol (0.8 mL) at room temperature. After stirring for 30 minutes, the reaction mixture was diluted with water and then extracted with chloroform (4 times), dried over anhydrous sodium sulfate, filtered and concentrated. Purification by flash chromatography on silica gel using 50% ethyl acetate in hexanes, ethyl acetate and 4% 2M ammonia in methanol in dichloromethane afforded the titled compound (23.8 mg, 77 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 8.04 (m, 1H), 7.93 (m, 1H), 7.68 (m, 2H), 7.42 (m, 2H), 7.03 (m, 2H), 4.37 (m, 1H), 4.07 (m, 2H), 3.89 (m, 3H), 3.82 (m, 2H), 3.11 (m, 1H), 2.88 (m, 1H), 2.56 (s, 3H).

## WE CLAIM:

1. A compound of formula I:



wherein

- $X^1, X^2, X^3, X^4,$  and  $X^5$  are independently selected from the group consisting of C, CR<sup>5</sup>, N, O, and S, wherein at least one of  $X^1, X^2, X^3, X^4,$  and  $X^5$  is not N;
- $X^6$  is selected from the group consisting of a bond and CR<sup>5</sup>R<sup>6</sup>;
- $X^7$  is CR<sup>5</sup> or N;
- $X^8$  is selected from the group consisting of a bond, CR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>, O, S, SO, and SO<sub>2</sub>;
- $X^9$  is CR<sup>5</sup> or N;
- $X^{10}$  is selected from the group consisting of a bond, CR<sup>5</sup>R<sup>6</sup>, (CR<sup>5</sup>R<sup>6</sup>)<sub>2</sub>, O, S, and NR<sup>5</sup>;
- $R^1$  is selected from the group consisting of hydroxy, halo, nitro, C<sub>1-6</sub>alkylhalo, OC<sub>1-6</sub>alkylhalo, C<sub>1-6</sub>alkyl, OC<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, OC<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, OC<sub>2-6</sub>alkynyl, C<sub>0-6</sub>alkylC<sub>3-6</sub>cycloalkyl, OC<sub>0-6</sub>alkylC<sub>3-6</sub>cycloalkyl, C<sub>0-6</sub>alkylaryl, OC<sub>0-6</sub>alkylaryl, CHO, (CO)R<sup>5</sup>, O(CO)R<sup>5</sup>, O(CO)OR<sup>5</sup>, O(CN)OR<sup>5</sup>, C<sub>1-6</sub>alkylOR<sup>5</sup>, OC<sub>2-6</sub>alkylOR<sup>5</sup>, C<sub>1-6</sub>alkyl(CO)R<sup>5</sup>, OC<sub>1-6</sub>alkyl(CO)R<sup>5</sup>, C<sub>0-6</sub>alkylCO<sub>2</sub>R<sup>5</sup>, OC<sub>1-6</sub>alkylCO<sub>2</sub>R<sup>5</sup>, C<sub>0-6</sub>alkylcyano, OC<sub>2-6</sub>alkylcyano, C<sub>0-6</sub>alkylNR<sup>5</sup>R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>R<sup>6</sup>, C<sub>1-6</sub>alkyl(CO)NR<sup>5</sup>R<sup>6</sup>, OC<sub>1-6</sub>alkyl(CO)NR<sup>5</sup>R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(CO)R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>(CO)R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(CO)NR<sup>5</sup>R<sup>6</sup>, C<sub>0-6</sub>alkylSR<sup>5</sup>, OC<sub>2-6</sub>alkylSR<sup>5</sup>, C<sub>0-6</sub>alkyl(SO)R<sup>5</sup>, OC<sub>2-6</sub>alkyl(SO)R<sup>5</sup>, C<sub>0-6</sub>alkylSO<sub>2</sub>R<sup>5</sup>, OC<sub>2-6</sub>alkylSO<sub>2</sub>R<sup>5</sup>, C<sub>0-6</sub>alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, OC<sub>2-6</sub>alkyl(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)R<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, OC<sub>2-6</sub>alkylNR<sup>5</sup>(SO<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, (CO)NR<sup>5</sup>R<sup>6</sup>, O(CO)NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>OR<sup>6</sup>, C<sub>0-6</sub>alkylNR<sup>5</sup>(CO)OR<sup>6</sup>, OC<sub>2-</sub>

$\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A;

$\text{R}^2$  is selected from the group consisting of hydrogen, hydroxy, halo, nitro,  $\text{C}_{1-6}\text{alkylhalo}$ ,  $\text{OC}_{1-6}\text{alkylhalo}$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{OC}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{OC}_{2-6}\text{alkynyl}$ ,  $\text{C}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{OC}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{C}_{0-6}\text{alkylaryl}$ ,  $\text{OC}_{0-6}\text{alkylaryl}$ ,  $\text{CHO}$ ,  $(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{OR}^5$ ,  $\text{O}(\text{CN})\text{OR}^5$ ,  $\text{C}_{1-6}\text{alkylOR}^5$ ,  $\text{OC}_{2-6}\text{alkylOR}^5$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylcyano}$ ,  $\text{OC}_{2-6}\text{alkylcyano}$ ,  $\text{C}_{0-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylSR}^5$ ,  $\text{OC}_{2-6}\text{alkylSR}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{NR}^5\text{OR}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A;

$\text{R}^3$  is a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A;

$\text{R}^4$  is selected from the group consisting of hydroxy, halo, nitro,  $\text{C}_{1-6}\text{alkylhalo}$ ,  $\text{OC}_{1-6}\text{alkylhalo}$ ,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{OC}_{1-6}\text{alkyl}$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{OC}_{2-6}\text{alkenyl}$ ,  $\text{C}_{2-6}\text{alkynyl}$ ,  $\text{OC}_{2-6}\text{alkynyl}$ ,  $\text{C}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{OC}_{0-6}\text{alkylC}_{3-6}\text{cycloalkyl}$ ,  $\text{C}_{0-6}\text{alkylaryl}$ ,  $\text{OC}_{0-6}\text{alkylaryl}$ ,  $\text{CHO}$ ,  $(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{OR}^5$ ,  $\text{O}(\text{CN})\text{OR}^5$ ,  $\text{C}_{1-6}\text{alkylOR}^5$ ,  $\text{OC}_{2-6}\text{alkylOR}^5$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{OC}_{1-6}\text{alkylCO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylcyano}$ ,  $\text{OC}_{2-6}\text{alkylcyano}$ ,  $\text{C}_{0-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5\text{R}^6$ ,  $\text{C}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{OC}_{1-6}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{CO})\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylSR}^5$ ,  $\text{OC}_{2-6}\text{alkylSR}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{C}_{0-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylSO}_2\text{R}^5$ ,  $\text{C}_{0-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{C}_{0-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{OC}_{2-6}\text{alkylNR}^5(\text{SO}_2)\text{R}^6$ .



$\text{C}_0\text{-6alkylNR}^5(\text{SO}_2)\text{R}^6$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^6$ ,  $(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^6$ ,  $\text{NR}^5\text{OR}^6$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5(\text{CO})\text{OR}^6$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S, wherein said ring may be substituted by one or more A;

$\text{R}^5$  and  $\text{R}^6$  are independently selected from the group consisting of hydrogen,  $\text{C}_1\text{-6alkyl}$ ,  $\text{C}_{3\text{-7}}\text{cycloalkyl}$  and aryl;

A is selected from the group consisting of hydrogen, hydroxy, halo, nitro,  $\text{C}_1\text{-6alkylhalo}$ ,  $\text{OC}_{1\text{-6}}\text{alkylhalo}$ ,  $\text{C}_1\text{-6alkyl}$ ,  $\text{OC}_{1\text{-6}}\text{alkyl}$ ,  $\text{C}_{2\text{-6}}\text{alkenyl}$ ,  $\text{OC}_{2\text{-6}}\text{alkenyl}$ ,  $\text{C}_{2\text{-6}}\text{alkynyl}$ ,  $\text{OC}_{2\text{-6}}\text{alkynyl}$ ,  $\text{C}_0\text{-6alkylC}_{3\text{-6}}\text{cycloalkyl}$ ,  $\text{OC}_{0\text{-6}}\text{alkylC}_{3\text{-6}}\text{cycloalkyl}$ ,  $\text{C}_0\text{-6alkylaryl}$ ,  $\text{OC}_{0\text{-6}}\text{alkylaryl}$ ,  $\text{CHO}$ ,  $(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{R}^5$ ,  $\text{O}(\text{CO})\text{OR}^5$ ,  $\text{O}(\text{CN})\text{OR}^5$ ,  $\text{C}_1\text{-6alkylOR}^5$ ,  $\text{OC}_{2\text{-6}}\text{alkylOR}^5$ ,  $\text{C}_1\text{-6alkyl}(\text{CO})\text{R}^5$ ,  $\text{OC}_{1\text{-6}}\text{alkyl}(\text{CO})\text{R}^5$ ,  $\text{C}_0\text{-6alkylCO}_2\text{R}^5$ ,  $\text{OC}_{1\text{-6}}\text{alkylCO}_2\text{R}^5$ ,  $\text{C}_0\text{-6alkylcyano}$ ,  $\text{OC}_{2\text{-6}}\text{alkylcyano}$ ,  $\text{C}_0\text{-6alkylNR}^5\text{R}^5$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5\text{R}^8$ ,  $\text{C}_1\text{-6alkyl}(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{OC}_{1\text{-6}}\text{alkyl}(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{CO})\text{R}^8$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5(\text{CO})\text{R}^8$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{C}_0\text{-6alkylSR}^5$ ,  $\text{OC}_{2\text{-6}}\text{alkylSR}^5$ ,  $\text{C}_0\text{-6alkyl}(\text{SO})\text{R}^5$ ,  $\text{OC}_{2\text{-6}}\text{alkyl}(\text{SO})\text{R}^5$ ,  $\text{C}_0\text{-6alkylSO}_2\text{R}^5$ ,  $\text{OC}_{2\text{-6}}\text{alkylSO}_2\text{R}^5$ ,  $\text{C}_0\text{-6alkyl}(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $\text{OC}_{2\text{-6}}\text{alkyl}(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{SO}_2)\text{R}^8$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5(\text{SO}_2)\text{R}^8$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5(\text{SO}_2)\text{NR}^5\text{R}^8$ ,  $(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{O}(\text{CO})\text{NR}^5\text{R}^8$ ,  $\text{NR}^5\text{OR}^8$ ,  $\text{C}_0\text{-6alkylNR}^5(\text{CO})\text{OR}^8$ ,  $\text{OC}_{2\text{-6}}\text{alkylNR}^5(\text{CO})\text{OR}^8$ ,  $\text{SO}_3\text{R}^5$  and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S;

n is 0, 1, 2, 3, or 4; or

a pharmaceutically acceptable salt or hydrate thereof;

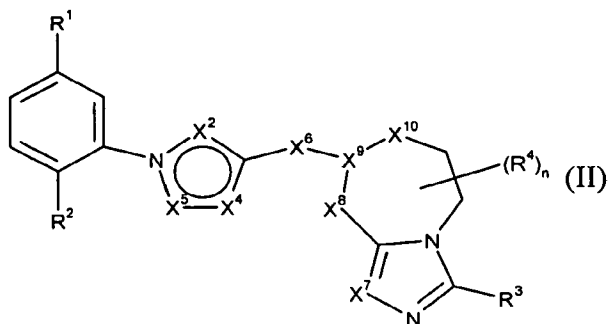
provided that the compound is not:

- 8-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine,
- 8-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-thiophen-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine,
- 8-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine,

8-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-3-pyridine-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-{1-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-[5-(5-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-3-furan-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
8-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
3-Pyridin-4-yl-8-[1-(5-m-tolyl-[1,2,4]oxadiazol-3-yl)-ethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine,  
(+)-8-{(1S)-1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidine,  
(-)-8-{(1R)-1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidine,  
3-[5-(3-Pyridin-4-yl-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl)[1,3,4]oxadiazol-2-yl]benzonitrile,  
3-{5-[3-(2-Methoxypyridin-4-yl)-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl][1,3,4]oxadiazol-2-yl}benzonitrile,  
3-{5-[3-(2-Methoxy-pyridin-4-yl)-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl]-[1,2,4]oxadiazol-3-yl}-benzonitrile,  
3-{3-[(3-pyridin-4-yl-6,7-dihydro[1,2,4]triazolo[4,3-a]pyrimidin-8(5H)-yl)methyl]-1,2,4-oxadiazol-5-yl}benzonitrile,  
3-(3-{[3-(2-methoxypyridin-4-yl)-6,7-dihydro[1,2,4]triazolo[4,3-a]pyrimidin-8(5H)-yl]methyl}-1,2,4-oxadiazol-5-yl)benzonitrile,  
3-{5-[(3-pyridin-4-yl-6,7-dihydro[1,2,4]triazolo[4,3-a]pyrimidin-8(5H)-yl)methyl]-1,2,4-oxadiazol-3-yl}benzonitrile, and

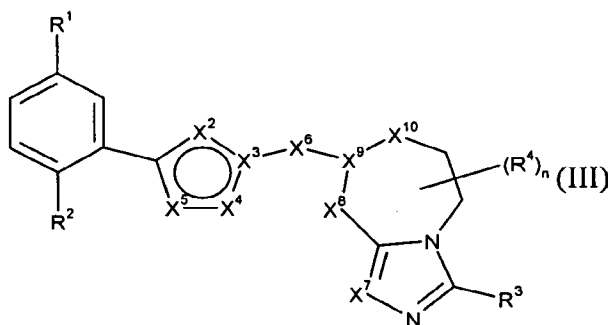
3-{5-[3-(2-Hydroxy-pyridin-4-yl)-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrimidin-8-ylmethyl]-[1,2,4]oxadiazol-3-yl}-benzonitrile.

2. The compound according to claim 1, of Formula II:



3. The compound according to claim 2, wherein  $X^7$  is N.

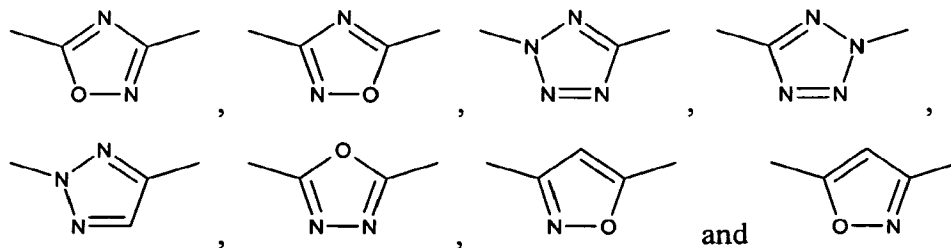
4. The compound according to claim 1, of Formula III:



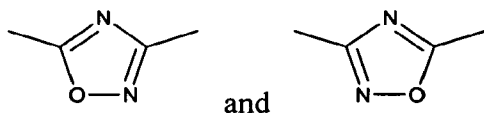
5. The compound according to claim 4, wherein  $X^3$  is C.

6. The compound according to claim 4, wherein  $X^3$  is N.

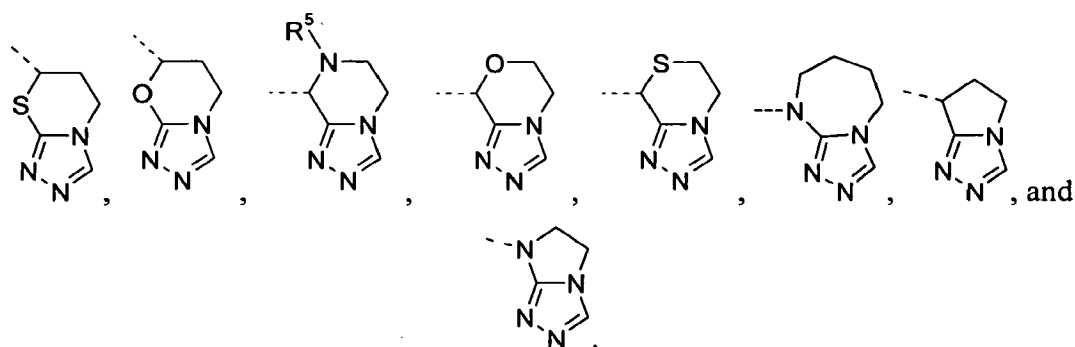
7. The compound according to claim 1, wherein the ring containing  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ , and  $X^5$  is selected from the group consisting of:



8. The compound according to claim 7, wherein the ring is selected from the group consisting of:



9. The compound according to claim 7, wherein  $X^7$  is N.
10. The compound according to claim 9, wherein  $X^8$  is a bond.
11. The compound according to claim 9, wherein  $X^8$  is S.
12. The compound according to claim 10, wherein  $X^9$  is  $CR^5$ .
13. The compound according to claim 12, wherein  $X^{10}$  is  $NR^5$ .
14. The compound according to claim 12, wherein  $X^{10}$  is O.
15. The compound according to claim 12, wherein  $X^{10}$  is  $CR^5R^6$ .
16. The compound according to claim 12, wherein  $X^{10}$  is  $(CR^5R^6)_2$ .
17. The compound according to claim 12, wherein  $X^{10}$  is a bond.
18. The compound according to claim 11, wherein  $X^9$  is  $CR^5$ .
19. The compound according to claim 18, wherein  $X^{10}$  is a bond.
20. The compound according to claim 11, wherein  $X^9$  is N.
21. The compound according to claim 7, wherein the fused ring containing  $X^7$ ,  $X^8$ ,  $X^9$ , and  $X^{10}$  is selected from the group consisting of:



22. The compound according to claim 1 selected from the group consisting of:
- 7-[5-(5-Chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-3-(2-thienyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3]thiazine,
- 9-{[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine,
- 9-{1-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]ethyl}-3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine,
- 7-{[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-3-pyridin-4-yl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole,
- 9-{[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a][1,3]diazepine,
- 8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine,
- 8-[3-(3-Chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3-(4-methoxy-phenyl)-7-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and
- pharmaceutically acceptable salts thereof.

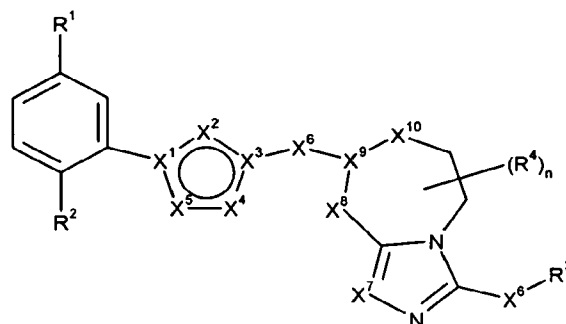
23. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound according to any one of claims 1 - 22, and one or more pharmaceutically acceptable diluents, excipients, and/or inert carriers.

24. The pharmaceutical composition according to claim 23, for use in the treatment of mGluR5-mediated disorders.

25. The compound according to any one of claims 1 - 22, for use in therapy.
26. The compound according to any one of claims 1 - 22, for use in the treatment of mGluR5-mediated disorders.
27. Use of the compound according to any one of claims 1 - 22 in the manufacture of a medicament for the treatment of mGluR5-mediated disorders.
28. A method for the treatment of mGluR5-mediated disorders, comprising administering to a mammal a therapeutically effective amount of the compound according to any one of claims 1 - 22.
29. The method according to claim 28, wherein the mammal is a human.
30. The method according to claim 28, wherein the disorder is a neurological disorder.
31. The method according to claim 28, wherein the disorder is a psychiatric disorder.
32. The method according to claim 28, wherein the disorders are selected from chronic and acute pain disorders.
33. The method according to claim 28, wherein the disorder is a gastrointestinal disorder.
34. A method for inhibiting activation of mGluR5 receptors, comprising contacting a cell containing said receptors with an effective amount of a compound according to any one of claims 1 - 22.

# ABSTRACT

The present invention is directed to compounds of formula I:



wherein  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$ ,  $X^8$ ,  $X^9$ ,  $X^{10}$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , and  $n$  are as defined  
 5 for formula I in the description. The invention also relates to processes for the preparation of the compounds and to new intermediates employed in the preparation, pharmaceutical compositions containing the compounds, and to the use of the compounds in therapy.

**Application Data Sheet****Application Information**

**Application Type::** Provisional  
**Subject Matter::** Utility  
**Suggested classification::**  
**Suggested Group Art Unit::**  
**CD-ROM or CD-R?::** None  
**Computer Readable Form (CRF)?::** No  
**Title::** FUSED HETEROCYCLIC COMPOUNDS AND  
THEIR USE AS METABOTROPIC GLUTAMATE  
RECEPTOR ANTAGONISTS  
**Attorney Docket Number::** 085747-0328  
**Request for Early Publication?::** No  
**Request for Non-Publication?::** No  
**Suggested Drawing Figure::**  
**Total Drawing Sheets::**  
**Small Entity?::** No  
**Petition included?::** No  
**Secrecy Order in Parent Appl.?::** No

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**Representative Information**

<b>Representative Customer Number::</b>	22428	
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**Domestic Priority Information**



Application::	Continuity Type::	Parent Application::	Parent Filing Date::

**Foreign Priority Information**

Country::	Application number::	Filing Date::	Priority Claimed::

**Assignee Information**

**Assignee name::**

AstraZeneca AB and NPS Pharmaceuticals, Inc.